Bard

Access DB# 97458

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: P. Spivack Examiner #: 76400 Date: 6/18/03
Art Unit: 1614 Phone Number 30 8-4703 Serial Number: 10/021,177
Mail Box and Bldg/Room Location: 2D01 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc. if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Modulation Stimulation Inhibition of Glutamate Reuptake

Inventors (please provide full names): Maria-Luisa Maccecchini
Pei Xue-Feng Include Inventors search

Earliest Priority Filing Date: 10/30/00

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search
methods of treating a disease involving glutamate levels
or
modulating, stimulating, or inhibiting
glutamate reuptake

comprising administer SYM 2081
SYM 2183
SYM 2062
SYM 2051

Thank

Thanks

****

STAFF USE ONLY		**Type of Search**		**Vendors and cost where applicable**	
Searcher:	ACB	NA Sequence (#)		STN	
Searcher Phone #:		AA Sequence (#)		Dialog	
Searcher Location:		Structure (#)		Questel/Orbit	
Date Searcher Picked Up:		Bibliographic	X	Dr.Link	
Date Completed:	6-25-03	Litigation		Lexis/Nexis	
Searcher Prep & Review Time:	15	Fulltext		Sequence Systems	
Clerical Prep Time:		Patent Family		WWW/Internet	
Online Time:	21	Other		Other (specify)	

PTO-1590 (8-01)

=> fil reg; d ide l10; d ide l11; d ide l12; d ide l13
FILE 'REGISTRY' ENTERED AT 11:28:13 ON 25 JUN 2003

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 24 JUN 2003 HIGHEST RN 536971-45-6
DICTIONARY FILE UPDATES: 24 JUN 2003 HIGHEST RN 536971-45-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

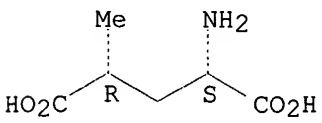
Registry records for 4 compounds

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

L10 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 31137-74-3 REGISTRY
CN .L-Glutamic acid, 4-methyl-, (4R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Glutamic acid, 4-methyl-, L-erythro- (8CI)
CN L-Glutamic acid, 4-methyl-, erythro-
OTHER NAMES:
CN (2S,4R)-4-Methylglutamic acid
CN erythro-.gamma.-Methyl-L-glutamic acid
CN erythro-.gamma.-Methylglutamic acid
CN erythro-L-4-Methylglutamic acid
CN L-erythro-.gamma.-Methylglutamate
CN L-erythro-.gamma.-Methylglutamic acid
CN **SYM 2081**
FS STEREOSEARCH
MF C6 H11 N O4
CI COM
LC STN Files: ADISINSIGHT, BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, CHEMCATS, CIN, CSCHEM, DRUGNL, DRUGUPDATES, PHAR, PROMT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).

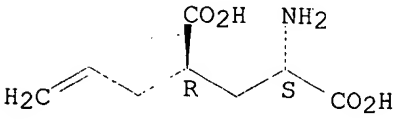


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

72 REFERENCES IN FILE CA (1957 TO DATE)
72 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L11 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 284024-46-0 REGISTRY
CN L-Glutamic acid, 4-(2-propenyl)-, (4R)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN LY 310214
CN **SYM 2083**
FS STEREOSEARCH
MF C8 H13 N O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry. Rotation (+).

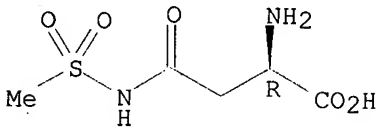


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L12 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 402578-67-0 REGISTRY
CN D-Asparagine, N-(methylsulfonyl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **SYM 2062**
FS STEREOSEARCH
MF C5 H10 N2 O5 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



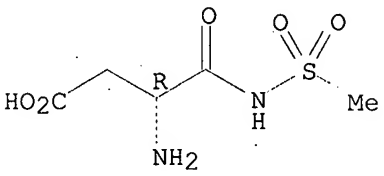
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L13 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 402578-41-0 REGISTRY
CN Butanoic acid, 3-amino-4-[(methylsulfonyl)amino]-4-oxo-, (3R)- (9CI) (CA INDEX NAME)

OTHER NAMES:
CN **SYM 2051**
FS STEREOSEARCH
MF C5 H10 N2 O5 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

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=> fil capl toxcenter uspatf; d que l17
FILE 'CAPLUS' ENTERED AT 11:39:42 ON 25 JUN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE 'TOXCENTER' ENTERED AT 11:39:42 ON 25 JUN 2003
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FILE 'USPATFULL' ENTERED AT 11:39:42 ON 25 JUN 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)


L11             1 SEA FILE=REGISTRY ABB=ON  "SYM 2083"/CN
L12             1 SEA FILE=REGISTRY ABB=ON  "SYM 2062"/CN
L13             1 SEA FILE=REGISTRY ABB=ON  "SYM 2051"/CN
L14             6 SEA L11
L15             5 SEA L12
L16             5 SEA L13
L17             6 SEA L14 OR L15 OR L16


=> dup rem l17
PROCESSING COMPLETED FOR L17
L18             5 DUP REM L17 (1 DUPLICATE REMOVED)
                  ANSWERS '1-3' FROM FILE CAPLUS
                  ANSWERS '4-5' FROM FILE USPATFULL

=> d ibib ab hitrn 1-5

L18  ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2003 ACS          DUPLICATE 1
ACCESSION NUMBER:         2002:391517  CAPLUS
DOCUMENT NUMBER:          136:395975
TITLE:                    Glutamate receptor ligands for modulation,
                          stimulation, and inhibition of glutamate transport
INVENTOR(S):              Maccecchini, Maria-Luisa; Pei, Xue-Feng
PATENT ASSIGNEE(S):       Annovis, Inc., USA
SOURCE:                   PCT Int. Appl., 48 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ----------------  ----  --------      ---------------  --------
     WO 2002040002      A2   20020523      WO 2001-US48448  20011030
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
             RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ,
             VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW:  GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     AU 2002037717      A5   20020527      AU 2002-37717    20011030
     US 2002188022      A1   20021212      US 2001-21177    20011030
PRIORITY APPLN. INFO.:                   US 2000-244252P  P  20001030
                                         WO 2001-US48448  W  20011030
OTHER SOURCE(S):          MARPAT 136:395975
AB   The invention discloses the use of glutamate receptor ligands (agonists
```

Registry # search

and antagonists) for inhibiting, stimulating, modulating, or regulating glutamate reuptake. It has been discovered that such compds. can bind to or modulate glutamate transporters and affect extracellular glutamate levels by affecting transporter activity. The disclosed compds. can have a variety of effects on glutamate transporter activity including activation or inhibition. Such compds. are useful to treat various neurol. diseases and conditions involving glutamate transporter and glutamate receptor activation. For example, excess extracellular glutamate is a cause of excessive activation of glutamate receptors. Stimulating glutamate reuptake by glutamate transporters can ameliorate excessive activation of glutamate receptors by reducing the extracellular glutamate concn. Prodrug forms of transporter compds. can be used as drugs.

IT **284024-46-0**, SYM 2083 **284024-46-0D**, derivs.
402578-41-0, SYM 2051 **402578-67-0**, SYM 2062
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glutamate receptor ligands for modulation, stimulation, and inhibition of glutamate transport)

L18 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:172225 CAPLUS
DOCUMENT NUMBER: 136:210595
TITLE: Screen for glutamate reuptake inhibitors, stimulators, and modulators
INVENTOR(S): Beart, Philip M.; O'Shea, Ross D.; Aprico, Karina; Lawrence, Andrew J.; Maccecchini, Maria-luisa
PATENT ASSIGNEE(S): Annovis, Inc., USA; Monash University
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018941	A2	20020307	WO 2001-US27323	20010831
WO 2002018941	A3	20020926		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001088658	A5	20020313	AU 2001-88658	20010831
EP 1314041	A2	20030528	EP 2001-968408	20010831
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002115688	A1	20020822	US 2001-944954	20010901

PRIORITY APPLN. INFO.: US 2000-229952P P 20000901
US 2000-230159P P 20000901
WO 2001-US27323 W 20010831

OTHER SOURCE(S): MARPAT 136:210595

AB Disclosed is a method for identifying compds. that bind to or modulate a glutamate transporter. The disclosed method is useful for identifying compds. that can inhibit, stimulate, or modulate the activity of the glutamate transporter and thus affect glutamate reuptake. The method is a screening technique where compds. known to bind to glutamate receptors (for example, glutamate receptor ligands, including many agonists, and

antagonists) are bound to a glutamate transporter and compds. are screened to identify those that can after the binding of the glutamate receptor-binding compds. Compds. shown to alter the binding of the receptor-binding compds. Compds. shown to alter the binding of the receptor compds. from glutamate transporter in the disclosed assay can have a variety of effects on glutamate transporter in the disclosed assay can have a variety of effects on glutamate transporter activity including activation or inhibition. These compds. are expected to affect or interfere with glutamate reuptake by the glutamate transporter and thus can be used to modulate, stimulate, or inhibit glutamate reuptake. Such compds. are useful to treat various neurol. diseases and conditions involving glutamate transporter and glutamate receptor activation. One of the compds. is (2S,4R)-4-methylglutamate or [3H]-(2S,4R)-4-methylglutamate. For example, excess extracellular glutamate is a cause of excessive activation of glutamate receptors. Stimulating glutamate reuptake by glutamate transporter can ameliorate excessive activation of glutamate receptors by reducing the extracellular glutamate concn. Prodrug forms of transporter compds. are preferred for use as drugs.

SYM 2081

IT **284024-46-0 402578-41-0 402578-67-0**
RL: PAC (Pharmacological activity); BIOL (Biological study)
(screening for glutamate reuptake inhibitors, stimulators, and modulators)

L18 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:321625 CAPLUS
DOCUMENT NUMBER: 133:99059
TITLE: 4-alkyl- and 4-cinnamylglutamic acid analogues are potent GluR5 kainate receptor agonists
AUTHOR(S): Pedregal, Concepcion; Collado, Ivan; Escribano, Ana; Ezquerra, Jesus; Dominguez, Carmen; Mateo, Ana I.; Rubio, Almudena; Baker, S. Richard; Goldsworthy, John; Kamboj, Rajender K.; Ballyk, Barbara A.; Hoo, Ken; Bleakman, David
CORPORATE SOURCE: Lilly S.A., Madrid, 28108, Spain
SOURCE: Journal of Medicinal Chemistry (2000), 43(10), 1958-1968
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Enantiomerically pure (2S,4R)-4-substituted glutamic acids were prepd. and tested for homomeric GluR5 and GluR6 kainate subtype receptor affinity. Some of the 4-cinnamyl analogs showed high selectivity and potency (Ki < 25 nM) for the GluR5 receptors. The greatest selectivity and potency were achieved with the 3-(2-naphthyl)prop-2-enyl compd. This compd., LY339434, has negligible activity at the AMPA and kainate receptors GluR1, -2, -4 and -6. Although, LY339434 shows agonist activity at NMDA receptors in cultural hippocampal neurons (approx. EC50 of 2.5 .mu.M), we consider that LY339434 should be a useful pharmacol. tool for the investigation of the functional role of GluR5 kainate receptors.

SYM 2083

IT **284024-46-0P**, LY 310214
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(alkyl- and cinnamylglutamic acid analogs are potent GluR5 kainate receptor agonists)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 4 OF 5 USPATFULL
ACCESSION NUMBER: 2002:330336 USPATFULL
TITLE: Methods for modulation, stimulation, and inhibition of glutamate reuptake

Searched by Barb O'Bryen, STIC 308-4291

INVENTOR(S): Maccecchini, Maria-Luisa, West Chester, PA, UNITED STATES
Pei, Xue-Feng, Lansdale, PA, UNITED STATES
PATENT ASSIGNEE(S): Annovis. Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002188022	A1	20021212
APPLICATION INFO.:	US 2001-21177	A1	20011030 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-244252P	20001030 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PATREA L. PABST, HOLLAND & KNIGHT LLP, SUITE 2000, ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, N.E., ATLANTA, GA, 30309-3400
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 13 Drawing Page(s)
LINE COUNT: 1053
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed is a method for inhibiting, stimulating, modulating, or regulating glutamate reuptake. The method makes use of compounds that are ligands of glutamate receptors, including many agonists, or antagonists of glutamate receptors. It has been discovered that such compounds can bind to or modulate glutamate transporters and affect extracellular glutamate levels by affecting transporter activity. The disclosed compounds can have a variety of effects on glutamate transporter activity including activation or inhibition. Such compounds are useful to treat various neurological diseases and conditions involving glutamate transporter and glutamate receptor activation. For example, excess extracellular glutamate is a cause of excessive activation of glutamate receptors. Stimulating glutamate reuptake by glutamate transporters can ameliorate excessive activation of glutamate receptors by reducing the extracellular glutamate concentration. Prodrug forms of transporter compounds can be used as drugs.

IT **284024-46-0**, SYM 2083 **284024-46-0D**, derivs.
402578-41-0, SYM 2051 **402578-67-0**, SYM 2062
(glutamate receptor ligands for modulation, stimulation, and inhibition of glutamate transport)

L18 ANSWER 5 OF 5 USPATFULL
ACCESSION NUMBER: 2002:214299 USPATFULL
TITLE: Screen for glutamate reuptake inhibitors, stimulators, and modulators
INVENTOR(S): Beart, Philip M., Ivanhoe, AUSTRALIA
O'Shea, Ross D., Blackburn South, AUSTRALIA
Aprico, Karina, Forest Hill, AUSTRALIA
Lawrence, Andrew J., Brighton, AUSTRALIA
Maccecchini, Maria-Luisa, West Chester, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002115688	A1	20020822
APPLICATION INFO.:	US 2001-944954	A1	20010901 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-229952P	20000901 (60)
	US 2000-230159P	20000901 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PATREA L. PABST, HOLLAND & KNIGHT LLP, SUITE 2000, ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, N.E., ATLANTA, GA, 30309-3400
NUMBER OF CLAIMS: 27
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 1184
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed is a method for identifying compounds that bind to or modulate a glutamate transporter. The disclosed method is useful for identifying compounds that can inhibit, stimulate, or modulate the activity of the glutamate transporter and thus affect glutamate reuptake. The method is a screening technique where compounds known to bind to glutamate receptors (for example, glutamate receptor ligands, including many agonists, and antagonists) are bound to a glutamate transporter and compounds are screened to identify those that can alter the binding of the glutamate receptor-binding compounds. Compounds shown to alter the binding of the receptor compounds from glutamate transporters in the disclosed assay can have a variety of effects on glutamate transporter activity including activation or inhibition. These compounds are expected to affect or interfere with glutamate reuptake by the glutamate transporter and thus can be used to modulate, stimulate, or inhibit glutamate reuptake. Such compounds are useful to treat various neurological diseases and conditions involving glutamate transporter and glutamate receptor activation. One of the compounds is (2S,4R)-4-methylglutamate or [.sup.3H]-(2S,4R)-4-methylglutamate. For example, excess extracellular glutamate is a cause of excessive activation of glutamate receptors. Stimulating glutamate reuptake by glutamate transporters can ameliorate excessive activation of glutamate receptors by reducing the extracellular glutamate concentration. Prodrug forms of transporter compounds are preferred for use as drugs.

IT **284024-46-0 402578-41-0 402578-67-0**
(screening for glutamate reuptake inhibitors, stimulators, and modulators)

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=> fil capl; d que l24; d que l29; s l24 or l29
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FILE COVERS 1907 - 25 Jun 2003  VOL 138 ISS 26
FILE LAST UPDATED: 24 Jun 2003  (20030624/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


L5        11863 SEA FILE=CAPLUS ABB=ON  GLUTAMATE RECEPTORS/CT
L8       256906 SEA FILE=CAPLUS ABB=ON  ?UPTAKE?
L10           1 SEA FILE=REGISTRY ABB=ON  "SYM 2081"/CN
L19          72 SEA FILE=CAPLUS ABB=ON  L10
L20           1 SEA FILE=REGISTRY ABB=ON  GLUTAMATE/CN
L21       86003 SEA FILE=CAPLUS ABB=ON  L20 OR GLUTAMATE#
L22          48 SEA FILE=CAPLUS ABB=ON  (L5 OR L21) AND L19
L24           5 SEA FILE=CAPLUS ABB=ON  L8 AND L22



L5        11863 SEA FILE=CAPLUS ABB=ON  GLUTAMATE RECEPTORS/CT
L10           1 SEA FILE=REGISTRY ABB=ON  "SYM 2081"/CN
L19          72 SEA FILE=CAPLUS ABB=ON  L10
L20           1 SEA FILE=REGISTRY ABB=ON  GLUTAMATE/CN
L21       86003 SEA FILE=CAPLUS ABB=ON  L20 OR GLUTAMATE#
L25       96279 SEA FILE=CAPLUS ABB=ON  NERVOUS SYSTEM/CW
L26      340576 SEA FILE=CAPLUS ABB=ON  BRAIN/CW
L27      142126 SEA FILE=CAPLUS ABB=ON  NERVE/CW
L28       78131 SEA FILE=CAPLUS ABB=ON  (L25 OR L26 OR L27)(L)(DISEASE# OR
                DISORDER#)
L29           7 SEA FILE=CAPLUS ABB=ON  L28 AND L19 AND (L5 OR L21)



L83          11 L24 OR L29

=> fil biosis; d que l32; fil toxcenter; d que l40; fil uspatf; d que l49; dup rem
l83,l32,l40,l49
FILE 'BIOSIS' ENTERED AT 12:22:42 ON 25 JUN 2003
COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC.(R)

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 19 June 2003 (20030619/ED)
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L10           1 SEA FILE=REGISTRY ABB=ON  "SYM 2081"/CN
L30          17 SEA FILE=BIOSIS ABB=ON  L10
L31       72397 SEA FILE=BIOSIS ABB=ON  GLUTAMATE#
L32           9 SEA FILE=BIOSIS ABB=ON  L30 AND L31


FILE 'TOXCENTER' ENTERED AT 12:22:42 ON 25 JUN 2003
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FILE COVERS 1907 TO 24 Jun 2003 (20030624/ED)

This file contains CAS Registry Numbers for easy and accurate substance
identification.

TOXCENTER has been enhanced with new files segments and search fields.
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TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the
MeSH 2003 vocabulary.  See http://www.nlm.nih.gov/mesh/summ2003.html
for a description on changes.


L10           1 SEA FILE=REGISTRY ABB=ON  "SYM 2081"/CN
L38          10 SEA FILE=TOXCENTER ABB=ON  L10
L39       39154 SEA FILE=TOXCENTER ABB=ON  GLUTAMATE#
L40           7 SEA FILE=TOXCENTER ABB=ON  L38 AND L39


FILE 'USPATFULL' ENTERED AT 12:22:42 ON 25 JUN 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 24 Jun 2003 (20030624/PD)
FILE LAST UPDATED: 24 Jun 2003 (20030624/ED)
HIGHEST GRANTED PATENT NUMBER: US6584613
HIGHEST APPLICATION PUBLICATION NUMBER: US2003115652
CA INDEXING IS CURRENT THROUGH 24 Jun 2003 (20030624/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 24 Jun 2003 (20030624/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2003
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2003

>>>  USPAT2 is now available.  USPATFULL contains full text of the     <<<
>>>  original, i.e., the earliest published granted patents or         <<<
>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent              <<<
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>>> the earliest to the latest publication. <<<

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L10           1 SEA FILE=REGISTRY ABB=ON  "SYM 2081"/CN
L49           3 SEA FILE=USPATFULL ABB=ON  L10


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PROCESSING COMPLETED FOR L32
PROCESSING COMPLETED FOR L40
PROCESSING COMPLETED FOR L49
L84           26 DUP REM L83 L32 L40 L49 (4 DUPLICATES REMOVED)
                 ANSWERS '1-11' FROM FILE CAPLUS
                 ANSWERS '12-20' FROM FILE BIOSIS
                 ANSWERS '21-23' FROM FILE TOXCENTER
                 ANSWERS '24-26' FROM FILE USPATFULL

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L84  ANSWER 1 OF 26  CAPLUS  COPYRIGHT 2003 ACS        DUPLICATE 1
ACCESSION NUMBER:         2002:391517  CAPLUS
DOCUMENT NUMBER:          136:395975
TITLE:                    Glutamate receptor ligands for modulation,
                          stimulation, and inhibition of glutamate
                          transport
INVENTOR(S):              Maccecchini, Maria-Luisa; Pei, Xue-Feng
PATENT ASSIGNEE(S):       Annovis, Inc., USA
SOURCE:                   PCT Int. Appl., 48 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ----------------  ----  --------      ---------------  --------
     WO 2002040002      A2   20020523      WO 2001-US48448  20011030
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
             RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ,
             VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
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AU 2002037717	A5	20020527	AU 2002-37717		20011030
US 2002188022	A1	20021212	US 2001-21177		20011030
PRIORITY APPLN. INFO.:			US 2000-244252P	P	20001030
			WO 2001-US48448	W	20011030

OTHER SOURCE(S): MARPAT 136:395975

AB The invention discloses the use of **glutamate** receptor ligands (agonists and antagonists) for inhibiting, stimulating, modulating, or regulating **glutamate reuptake**. It has been discovered that such compds. can bind to or modulate **glutamate** transporters and affect extracellular **glutamate** levels by affecting transporter activity. The disclosed compds. can have a variety of effects on **glutamate** transporter activity including activation or inhibition. Such compds. are useful to treat various neurol. diseases and conditions involving **glutamate** transporter and **glutamate** receptor activation. For example, excess extracellular **glutamate** is a cause of excessive activation of **glutamate** receptors. Stimulating **glutamate reuptake** by **glutamate** transporters can ameliorate excessive activation of **glutamate** receptors by reducing the extracellular **glutamate** concn. Prodrug forms of transporter compds. can be used as drugs.

IT **31137-74-3**, SYM 2081
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**glutamate** receptor ligands for modulation, stimulation, and inhibition of **glutamate** transport)

L84 ANSWER 2 OF 26 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 2

ACCESSION NUMBER:	2000:182659 CAPLUS
DOCUMENT NUMBER:	132:289094
TITLE:	Low-affinity kainate receptor agonists induce insult-dependent apoptosis and necrosis in cultured murine cortical neurons
AUTHOR(S):	Moldrich, Randal X.; Beart, Philip M.; Pascoe, Catherine J.; Cheung, Nam S.
CORPORATE SOURCE:	Department of Pharmacology, Monash University, Clayton, 3168, Australia
SOURCE:	Journal of Neuroscience Research (2000), 59(6), 788-796 CODEN: JNREDK; ISSN: 0360-4012
PUBLISHER:	Wiley-Liss, Inc.
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Overstimulation of ionotropic **glutamate** receptors leads to excitotoxic neuronal death, which has been implicated in the neurodegeneration of neurol. diseases. The present study examd. the role of putative low-affinity kainate receptor subtype (GluR5-7) agonists in excitotoxicity in cultured murine cortical neurons. The concn.-dependent decrease in cell viability induced by the agonists kainate (1-1000 .mu.M) and (RS)-2-amino-3-(hydroxy-5-tert-butylisoxazol-4-yl) propanoic acid (ATPA; 1-1000 .mu.M) was only attenuated by 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; 10 .mu.M) and 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (GYKI 52466; 20 .mu.M). (S)-5-iodowillardiine (1-1000 .mu.M)-induced toxicity was attenuated by CNQX (20 .mu.M), GYKI 52466 (20 .mu.M) and MK-801 (10 .mu.M); however, (2S,4R)-4-methylglutamate (1-120 .mu.M)-induced toxicity was not attenuated by the antagonists. None of the agonists possessed selective actions at GluR5-7. Morphol. observations (phase-contrast and fluorescence microscopy) revealed that the agonists induced two distinct patterns of neuronal injury. After 24 h of treatment, low concns. of agonists (1-30 .mu.M) produced cellular shrinkage and nuclear granulation consistent with slow, apoptotic-like neuronal death. Pyknotic labeling with the DNA binding dye Sytox green confirmed these apoptotic characteristics, which significantly decreased with increasing concns. After 4 h, increasing concns. of agonists

(100-1000 .mu.M) induced cellular swelling, with subsequent extracellular debris; labeling with propidium iodide revealed isolated nuclei consistent with the increased involvement of rapid necrosis. Thus, all putative GluR5-7 agonists produced excitotoxicity across a necrotic-apoptotic continuum in murine cortical neuron cultures.

IT **31137-74-3**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(low-affinity kainate receptor agonists induce insult-dependent apoptosis and necrosis in cultured murine cortical neurons)

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 3 OF 26 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 3
ACCESSION NUMBER: 1999:567887 CAPLUS
DOCUMENT NUMBER: 131:281448
TITLE: Excitotoxic injury profiles of low-affinity kainate receptor agonists in cortical neuronal cultures
AUTHOR(S): Moldrich, Randal X.; Cheung, Nam S.; Pascoe, Catherine J.; Beart, Philip M.
CORPORATE SOURCE: Department of Pharmacology, Monash University, Clayton, 3168, Australia
SOURCE: European Journal of Pharmacology (1999), 378(2), R1-R3
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Neurotoxic profiles of putative agonists for low-affinity kainate subtypes of L-**glutamate** receptors (GluR5-7) were detd. in cultured cortical neurons. Rank order of neurotoxic potency (.mu.M): (S)-5-iodowillardiine (9) .apprxeq. (2S,4R,6E)-2-amino-4-carboxy-7-(2-naphthyl)hept-6-enoic acid (LY339434, 11) > (2S,4R)-4-methylglutamate (33) > kainate (100) > (RS)-2-amino-3-(hydroxy-5-tert-butylisoxazol-4-yl)propanoic acid (ATPA, 360). Using ionotropic **glutamate** receptor antagonists, neurotoxicity induced by kainate, ATPA and (S)-5-iodowillardiine appeared to involve a GluR5-7 component, unlike LY339434 and (2S,4R)-4-methylglutamate. These putative GluR5-7 agonists exhibited complex excitotoxic profiles highlighting the importance of studying native **glutamate** receptors.

IT **31137-74-3**, (2S,4R)-4-Methylglutamic acid
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(excitotoxic injury profiles of low-affinity kainate receptor agonists in cortical neuronal cultures)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 4 OF 26 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 4
ACCESSION NUMBER: 1993:140037 CAPLUS
DOCUMENT NUMBER: 118:140037
TITLE: **Glutamate uptake** system in the presynaptic vesicle: Glutamic acid analogs as inhibitors and alternate substrates
AUTHOR(S): Winter, Harry C.; Ueda, Tetsufumi
CORPORATE SOURCE: Med. Sch., Univ. Michigan, Ann Arbor, MI, 48109, USA
SOURCE: Neurochemical Research (1993), 18(1), 79-85
CODEN: NEREDZ; ISSN: 0364-3190
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A variety of naturally occurring amino acids, their isomers, and synthetic analogs were tested for their ability to inhibit **uptake** of [3H] **glutamate** into presynaptic vesicles from bovine cerebral cortex. Strongest inhibition (Ki <1 mM) was obsd. for trans-1-aminocyclopentane-

1,3-dicarboxylic acid (t-ACPD) and erythro-4-methyl-L-glutamic acid (MGlu), while 4-methylene-L-glutamic acid (MeGlu) was only moderately inhibitory (Ki = .apprx.3 mM), indicating that the synaptic vesicle **glutamate** translocator has higher affinity for trans-ACPD and MGlu than for **glutamate**. A few other amino acids, e.g., 4-hydroxyglutamic acid, S-carboxyethyl cysteine, and 5-fluorotryptophan, were slightly inhibitory; all L- and DL-isomers of protein amino acids and longer chain acidic amino acids were without measurable inhibition. Potassium tetrathionate and S-sulfocysteine exhibited strong to moderate noncompetitive or irreversible inhibition. Inhibition by t-ACPD, MGlu, or MeGlu was competitive with glutamic acid. Each of these competitive inhibitors was also taken up by the vesicle prepn. in an ATP-dependent manner, as indicated by their being recovered unchanged from filtered vesicles. Similar results were obtained with reconstituted vesicles, while **glutamate uptake** by partially purified rat synaptosomes was inhibited only by MGlu. These results indicate that the **glutamate** translocator of presynaptic vesicles has stringent structural requirements distinct from those of the plasma membrane translocator and the metabotropic type of postsynaptic **glutamate** receptor. They further suggest possible structural requirements of pharmacol. significant compds. that can substitute for glutamic acid in the presynaptic side of glutamatergic synapses, thus serving to moderate or control **glutamate** excitation and assocd. excitotoxic effects in these neurons.

IT **31137-74-3**
RL: BIOL (Biological study)
(as **glutamate uptake** system inhibitors and alternate substrates, in cerebral cortex presynaptic vesicles, structure in relation to)

L84 ANSWER 5 OF 26 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:172225 CAPLUS
DOCUMENT NUMBER: 136:210595
TITLE: Screen for **glutamate reuptake** inhibitors, stimulators, and modulators
INVENTOR(S): Beart, Philip M.; O'Shea, Ross D.; Aprico, Karina; Lawrence, Andrew J.; Maccecchini, Maria-luisa
PATENT ASSIGNEE(S): Annovis, Inc., USA; Monash University
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018941	A2	20020307	WO 2001-US27323	20010831
WO 2002018941	A3	20020926		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001088658	A5	20020313	AU 2001-88658	20010831
EP 1314041	A2	20030528	EP 2001-968408	20010831
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002115688	A1	20020822	US 2001-944954	20010901

PRIORITY APPLN. INFO.: US 2000-229952P P 20000901
US 2000-230159P P 20000901
WO 2001-US27323 W 20010831

OTHER SOURCE(S): MARPAT 136:210595

AB Disclosed is a method for identifying compds. that bind to or modulate a **glutamate** transporter. The disclosed method is useful for identifying compds. that can inhibit, stimulate, or modulate the activity of the **glutamate** transporter and thus affect **glutamate reuptake**. The method is a screening technique where compds. known to bind to **glutamate** receptors (for example, **glutamate** receptor ligands, including many agonists, and antagonists) are bound to a **glutamate** transporter and compds. are screened to identify those that can after the binding of the **glutamate** receptor-binding compds. Compds. shown to alter the binding of the receptor-binding compds. Compds. shown to alter the binding of the receptor compds. from **glutamate** transporter in the disclosed assay can have a variety of effects on **glutamate** transporter in the disclosed assay can have a variety of effects on **glutamate** transporter activity including activation or inhibition. These compds. are expected to affect or interfere with **glutamate reuptake** by the **glutamate** transporter and thus can be used to modulate, stimulate, or inhibit **glutamate reuptake**. Such compds. are useful to treat various neurol. diseases and conditions involving **glutamate** transporter and **glutamate** receptor activation. One of the compds. is (2S,4R)-4-methylglutamate or [3H]-(2S,4R)-4-methylglutamate. For example, excess extracellular **glutamate** is a cause of excessive activation of **glutamate** receptors. Stimulating **glutamate reuptake** by **glutamate** transporter can ameliorate excessive activation of **glutamate** receptors by reducing the extracellular **glutamate** concn. Prodrug forms of transporter compds. are preferred for use as drugs.

IT **31137-74-3**
RL: PAC (Pharmacological activity); BIOL (Biological study)
(screening for **glutamate reuptake** inhibitors, stimulators, and modulators)

L84 ANSWER 6 OF 26 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:651760 CAPLUS
DOCUMENT NUMBER: 136:95915
TITLE: Excitotoxic profiles of novel, low-affinity kainate receptor agonists in primary cultures of murine cerebellar granule cells
AUTHOR(S): Giardina, S. F.; Beart, P. M.
CORPORATE SOURCE: Department of Pharmacology, Monash University, Clayton, 3800, Australia
SOURCE: Neuropharmacology (2001), 41(4), 421-432
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The involvement of low-affinity kainate (KA) receptors in neuronal injury was investigated by employing a variety of agonists active at GluR5-7. Their excitotoxic profiles were detd. in primary cultures of cerebellar granule cells, which abundantly expressed low-affinity KA receptors, and in the absence of any AMPA receptor-mediated neurotoxicity. Neurotoxicity induced by these compds. was analyzed by phase contrast microscopy, a cell viability assay, the TUNEL technique (apoptosis), and by employing propidium iodide (PI; necrosis). All agonists induced concn.-dependent neurotoxicity, with rank order (EC50 values; .mu.M): (S)-iodowillardiine (IW) 0.2> (2S,4R)-4-methylglutamate (4-MG) 36>(2S,4R,6E)-2-amino-4-carboxy-7-(2-naphthyl)hept-6-enoic acid (LY339434) 46>KA 74> (RS)-2-amino-3-(3-hydroxy-5-tert-butylisoxazol-4-yl)propanoic acid (ATPA) 88. IW exposure resulted in apoptosis at lower concns. (<30 .mu.M) and necrosis at higher

concns., both of which were attenuated by CNQX (50 .mu.M), but not MK-801 (10 .mu.M). ATPA-mediated neurotoxicity was purely apoptotic and was attenuated by the non-NMDA receptor antagonists. Both IW and ATPA induced injury with the morphol. characteristics of apoptosis shown by the presence of TUNEL-pos. neurons. LY339434-mediated neuronal injury was only attenuated by MK-801 and was necrotic in nature. Similarly, 4-MG (>30 .mu.M) exposure caused necrosis that was partially attenuated by MK-801 (10 .mu.M) and CNQX (50 .mu.M). The patterns of neurotoxicity possessed a complex pharmacol. profile, demonstrated an apoptotic-necrotic continuum and were inconsistent with past findings, further outlining the importance of characterizing novel compds. at native receptors. ATPA and to a lesser extent IW appear to be suitable drugs for low-affinity KA receptors. Since toxicity-mediated by low-affinity KA receptors seem likely to contribute to neurodegenerative conditions, our study importantly examines the excitotoxic profile of these novel agonists.

IT **31137-74-3**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(excitotoxic profiles of novel, low-affinity kainate receptor agonists in primary cultures of murine cerebellar granule cells)

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 7 OF 26 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:142167 CAPLUS
DOCUMENT NUMBER: 132:306711
TITLE: SYM-2081 a kainate receptor antagonist reduces allodynia and hyperalgesia in a freeze injury model of neuropathic pain
AUTHOR(S): Ta, L. E.; Dionne, R. A.; Fricton, J. R.; Hodges, J. S.; Kajander, K. C.
CORPORATE SOURCE: Department of Diagnostic and Surgical Sciences, University of Minnesota, Minneapolis, MN, USA
SOURCE: Brain Research (2000), 858(1), 106-120
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cold-freeze injury at -4.degree.C to the rat sciatic nerve produces mech. allodynia and thermal hyperalgesia. The NMDA receptor, an excitatory amino acid (EAA) receptor, appears to be involved in the development of allodynia and hyperalgesia following nerve injury. The role, if any, of the kainate receptor, another EAA receptor, remains unknown. In the current study, the authors evaluated whether (2S,4R)-4-methylglutamic acid (SYM-2081), a recently developed kainate receptor antagonist, attenuates increased responsiveness following cold injury to the sciatic nerve. During baseline testing, Sprague-Dawley rats were evaluated for frequency of withdrawal from von Frey filaments and latency of withdrawal from a radiant thermal source. Animals were then anesthetized, the left sciatic nerve was exposed, and the nerve was cooled to -4.degree.C for 15 min (n=24). For control rats (n=24), all procedures were identical except that the nerve was maintained at 37.degree.C. Testing resumed on the third day following surgery. On the fifth post-operative day, SYM-2081 (150 or 100 mg/kg), fentanyl citrate (0.04 mg/kg) or vehicle was injected i.p. Injury to the rat sciatic nerve induced a significant increase in withdrawal frequency and a significant decrease in withdrawal latency (ANOVA, $p<0.05$). SYM-2081 and fentanyl significantly reduced these responses ($p<0.05$). These results suggest that kainate and opioid receptors are involved in the mech. allodynia and thermal hyperalgesia that develop following cold injury to the sciatic nerve.

IT **31137-74-3**, SYM-2081
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(kainate receptor and opioid receptor involvement in allodynia and hyperalgesia in freeze injury model of neuropathic pain and therapeutic potential of receptor antagonists)
REFERENCE COUNT: 114 THERE ARE 114 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 8 OF 26 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:256215 CAPLUS
DOCUMENT NUMBER: 131:53927
TITLE: The kainate receptor antagonist 2S,4R-4-methylglutamate attenuates mechanical allodynia and thermal hyperalgesia in a rat model of nerve injury
AUTHOR(S): Sutton, J. L.; Maccecchini, M.-L.; Kajander, K. C.
CORPORATE SOURCE: Department of Oral Science, and Graduate Program in Neuroscience, University of Minnesota, Minneapolis, MN, 55455, USA
SOURCE: Neuroscience (Oxford) (1999), 91(1), 283-292
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Opioids and receptor antagonists of excitatory amino acids attenuate mech. allodynia and thermal hyperalgesia in animal models of neuropathic pain. Recently, a kainate receptor antagonist, 2S,4R-4-methylglutamate, has been developed but has not been tested for antinociceptive effects in animal models of neuropathic pain. We evaluated whether 2S,4R-4-methylglutamate attenuated responses to mech. and thermal stimuli in uninjured (control) rats and increased responsiveness in rats with chronic constriction injury. Rats were tested for a no. of withdrawal responses using a calibrated von Frey filament (mech. stimulus) and withdrawal latencies from a radiant heat source (thermal stimulus). In control rats, 2S,4R-4-methylglutamate produced a small but significant decrease in responses from the mech. stimulus (25 mg/kg) and significantly increased withdrawal latencies from the thermal stimulus at the highest dose administered (100 mg/kg). In addn., 2S,4R-4-methylglutamate greatly attenuated increased responsiveness in rats with chronic constriction injury. At four to eight days following chronic constriction injury, animals that displayed increased responsiveness to mech. and thermal stimuli were injected i.p. with either dizocilpine maleate (0.1 mg/kg), morphine (4 mg/kg), vehicle as controls, or 2S,4R-4-methylglutamate (25, 50, 75 or 100 mg/kg). 2S,4R-4-Methylglutamate (25, 50, 75 and 100 mg/kg) significantly attenuated the frequency of responses to mech. stimuli (Wilcoxon, $P < 0.05$) and the latency of responses to thermal stimuli (anal. of variance and Duncan's, $P < 0.05$). Dizocilpine maleate and morphine, as expected, also reduced these responses. These results suggest that, in addn. to opioid and N-methyl-D-aspartate receptors, kainate receptors may play a role in the maintenance of mech. allodynia and thermal hyperalgesia assocd. with peripheral nerve injury.
IT **31137-74-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(2S,4R-4-methylglutamate attenuation of and receptor mediation of mech. allodynia and thermal hyperalgesia in nerve injury)
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 9 OF 26 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:339244 CAPLUS
DOCUMENT NUMBER: 133:221159
TITLE: Low-affinity kainate receptor subunit-specific agonist, (2S,4R)-4-methylglutamate (SYM-2081), does

not induce neuronal cell death in rat hippocampal formation
AUTHOR(S): Okazaki, Mitsuhiro; Kitamura, Yoshihisa; Matsuoka, Yasuji
CORPORATE SOURCE: Department of Neurobiology, Kyoto Pharmaceutical University, Kyoto, 607-8412, Japan
SOURCE: Journal of Brain Science (1999), 25(1 & 2), 3-10
CODEN: JBSCF5; ISSN: 1341-5301
PUBLISHER: PJD Publications Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Kainic acid (KA) induces neuronal cell death and glial activation in the hippocampal CA3 subfield of rat brain. This neuronal and glial activation is partly mediated by activation of the kainate receptor. The kainate receptors were divided into low- and high-affinity kainate receptor subunits, GluR5-7 and KA1/2, resp. In this study, we tried to clarify how low-affinity kainate receptor subunits participate in neurodegeneration using the specific agonist (2S, 4R)-4-methylglutamate (SYM-2081) by a comparison with KA. In this study, KA induced neuronal death, activation of microglia, and the transient loss of astrocytes. In contrast, the injection of SYM-2081 did not affect neurons or glia. Phosphorylation of c-Jun, an important step in neuronal apoptosis, was obsd. after the injection of KA. However, SYM-2081 did not phosphorylate c-Jun. These results suggest that the low-affinity kainate receptor subunits were less important for neuronal and glial activation, and that the high-affinity kainate receptor subunits may play more crit. roles in KA-induced neurodegeneration.
IT **31137-74-3**, SYM-2081
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(low-affinity kainate receptor subunits role in neurodegeneration)
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 10 OF 26 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:154392 CAPLUS
DOCUMENT NUMBER: 128:278857
TITLE: A novel kainate receptor ligand [3H]-(2S,4R)-4-methylglutamate: pharmacological characterization in rabbit brain membranes
AUTHOR(S): Toms, N. J.; Reid, M. E.; Phillips, W.; Kemp, M. C.; Roberts, P. J.
CORPORATE SOURCE: Department of Pharmacology, School of Medical Sciences, University of Bristol, Bristol, BS8 1TD, UK
SOURCE: Neuropharmacology (1998), Volume Date 1997, 36(11/12), 1483-1488
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Since kainate evokes large non-desensitizing currents at .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, kainate is of limited use in discriminating between AMPA and kainate receptors. Following recent reports that (2S,4R)-4-methylglutamate is a kainate receptor-selective agonist, we have radiolabeled and subsequently characterized the binding of [3H]-(2S,4R)-4-methylglutamate to rabbit whole-brain membranes. [3H]-(2S,4R)-4-methylglutamate binding was rapid, reversible and labeled two sites (KD1 = 3.67 .+-. 0.50 nM/Bmax1 = 0.54 .+-. 0.03 pmol/mg protein and KD2 = 281.66 .+-. 12.33 nM/Bmax2 = 1.77 .+-. 0.09 pmol/mg protein). [3H]-(2S,4R)-4-methylglutamate binding was displaced by several non-NMDA receptor ligands: domoate > kainate .mchgt. L-quisqualate .gtoreq. L-**glutamate** > 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) .mchgt. (S)-AMPA = (S)-5-fluorowillardiine > NMDA. Neither the metabotropic

glutamate receptor agonists (1S,3R)-ACPD or L-AP4, together with the L-**glutamate uptake** inhibitor L-trans-2,4-PDC, influenced binding when tested at 100 .mu.M. We conclude that [3H]-(2S,4R)-4-methylglutamate is a useful radioligand for labeling kainate receptors. It possesses high selectivity, and possesses a pharmacol. similar to that for rat cloned low-affinity (Glu5 and 6) kainate receptor subunits.

IT **31137-74-3**, (2S,4R)-4-Methylglutamic acid
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. in brain membranes of [3H]-(2S,4R)-4-methylglutamate as selective kainate receptor ligand)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 11 OF 26 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:129242 CAPLUS
DOCUMENT NUMBER: 128:252839
TITLE: DL-threo-.beta.-Benzyloxyaspartate, a potent blocker of excitatory amino acid transporters
AUTHOR(S): Shimamoto, Keiko; Lebrun, Bruno; Yasuda-Kamatani, Yoshimi; Sakaitani, Masahiro; Shigeri, Yasushi; Yumoto, Noboru; Nakajima, Terumi
CORPORATE SOURCE: Suntory Institute for Bioorganic Research, Osaka, 618, Japan
SOURCE: Molecular Pharmacology (1998), 53(2), 195-201
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB DL-Threo-.beta.-Benzyloxyaspartate (DL-TBOA), a novel deriv. of DL-threo-.beta.-hydroxyaspartate, was synthesized and examd. as an inhibitor of sodium-dependent **glutamate**/aspartate (excitatory amino acid) transporters. DL-TBOA inhibited the **uptake** of [14C] **glutamate** in COS-1 cells expressing the human excitatory amino acid transporter-1 (EAAT1) (Ki = 42 .mu.M) with almost the same potency as DL-threo-.beta.-hydroxyaspartate (Ki = 58 .mu.M). With regard to the human excitatory amino acid transporter-2 (EAAT2), the inhibitory effect of DL-TBOA (Ki = 5.7 .mu.M) was much more potent than that of dihydrokainate (Ki = 79 .mu.M), which is well known as a selective blocker of this subtype. Electrophysiol., DL-TBOA induced no detectable inward currents in Xenopus laevis oocytes expressing human EAAT1 or EAAT2. However, it significantly reduced the **glutamate**-induced currents, indicating the prevention of transport. The dose-response curve of **glutamate** was shifted by adding DL-TBOA without a significant change in the max. current. The Kb values for human EAAT1 and EAAT2 expressed in X. laevis oocytes were 9.0 .mu.M and 116 nM, resp. These results demonstrated that DL-TBOA is, so far, the most potent competitive blocker of **glutamate** transporters. DL-TBOA did not show any significant effects on either the ionotropic or metabotropic **glutamate** receptors. Moreover, DL-TBOA is chem. much more stable than its benzoyl analog, a previously reported blocker of excitatory amino acid transporters; therefore, DL-TBOA should be a useful tool for investigating the physiol. roles of transporters.

IT **31137-74-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(DL-threo-.beta.-benzyloxyaspartate, a potent blocker of excitatory amino acid transporters)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 12 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2003:135828 BIOSIS
DOCUMENT NUMBER: PREV200300135828
TITLE: Low-affinity kainate receptor-mediated events reduce the protective activity of phenobarbital and diphenylhydantoin against maximal electroshock in mice.
AUTHOR(S): Borowicz, K. K.; Zadrozniak, M.; Czuczwar, S. J. (1)
CORPORATE SOURCE: (1) Department of Pathophysiology, Lublin Medical University, Jaczewskiego 8, Lublin, 20-090, Poland: czuczwar@galen.imw.lublin.pl Poland
SOURCE: Neuropharmacology, (December 2002, 2002) Vol. 43, No. 7, pp. 1082-1086. print.
ISSN: 0028-3908.
DOCUMENT TYPE: Article
LANGUAGE: English
AB (2S,2R)-4-Methylglutamic acid (SYM 2081), a potent selective agonist of GluR5 and GluR6 kainate receptor subtypes, applied at the dose of 15.5 mg/kg, equal to its CD16 value (i.e., a dose required to induce convulsions in 16% of mice), significantly decreased the electroconvulsive threshold from 7.0 to 5.8 mA. When administered at the dose of 11.5 mg/kg, equal to 75% of its CD16, it markedly attenuated the protective activity of phenobarbital and diphenylhydantoin, but not that of valproate, carbamazepine, or diazepam against maximal electroshock-induced seizures in mice. The respective ED50 values were increased from 18.5 to 23.8 mg/kg for phenobarbital, and from 11.7 to 14.7 mg/kg for diphenylhydantoin. Since the free plasma levels of both antiepileptic drugs were not influenced by SYM 2081, the pharmacokinetic interaction does not seem to be involved in the observed results. In conclusion, low-affinity kainate receptor-mediated events might be a factor reducing the protective efficacy of some antiepileptic drugs. Furthermore, the activation of GluR5 and GluR6 kainate receptor subtypes by endogenous **glutamate** during seizures may be associated with the drug-resistance phenomenon.

L84 ANSWER 13 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:282284 BIOSIS
DOCUMENT NUMBER: PREV200300282284
TITLE: AMPA RATHER THAN KAINATE RECEPTORS MEDIATE ACETYLCHOLINE RELEASE FROM RABBIT RETINA.
AUTHOR(S): Firth, S. I. (1); Massey, S. C.; Li, W.; Marshak, D. W. (1)
CORPORATE SOURCE: (1) Neurobiol. and Anatomy, UT-Med School, Houston, TX, USA USA
SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 158.2. http://sfn.scholarone.com. cd-rom.
Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience Orlando, Florida, USA November 02-07, 2002 Society for Neuroscience
.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Cholinergic amacrine cells are a major type of local circuit neuron in the mammalian retina. Excitatory input to the cholinergic amacrine cells is via **glutamate** receptors of the AMPA/kainate type (Linn et al, 1991). The goal was to determine which receptor subtypes mediate this response. An in vivo, rabbit eyecup was preloaded with (3H)-choline, and the (3H)-ACh released into the superfusate was monitored (Massey & Redburn, 1982). A photopic, 3 Hz flash increased ACh release, and this light response was blocked by the specific AMPA receptor antagonists, GYKI 53655. Nonselective AMPA/kainate agonists also increased the release of ACh, but the specific kainate receptor agonist, SYM 2081 did not increase ACh release. We concluded that the excitatory input due to the light stimulus is mediated by AMPA receptors. We labeled lightly fixed retinas with antisera to either GluR 1, GluR 2/3 or GluR 4, the subunits found in AMPA receptors and ChAT. Many labeled punctae were observed in the inner

plexiform layer with each of the GluR antisera. However, there were no GluR 1-IR punctae on ChAT-IR dendrites. There were a few GluR 2/3-IR punctae, but more commonly, GluR 4-IR punctae were found on the ChAT-IR dendrites. The same was true of dye-injected cholinergic cells. Based on studies of recombinant AMPA receptor subunits, excitatory synapses where GluR 4 predominate are expected to be particularly strong (Swanson et al, 1997). Generally responses of AMPA receptors to **glutamate** rapidly desensitize and recover from desensitization, and this may account, at least in part, for the sensitivity of cholinergic cells to moving stimuli (O'Malley & Masland, 1993).

L84 ANSWER 14 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:509712 BIOSIS
DOCUMENT NUMBER: PREV200100509712
TITLE: Presynaptic kainate receptors at hippocampal mossy fiber synapses.
AUTHOR(S): Schmitz, Dietmar; Mellor, Jack; Frerking, Matthew; Nicoll, Roger A. (1)
CORPORATE SOURCE: (1) Departments of Cellular and Molecular Pharmacology and Physiology, University of California, San Francisco, CA, 94143: nicoll@phy.ucsf.edu USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (September 25, 2001) Vol. 98, No. 20, pp. 11003-11008. print.
ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Hippocampal mossy fibers, which are the axons of dentate granule cells, form powerful excitatory synapses onto the proximal dendrites of CA3 pyramidal cells. It has long been known that high-affinity binding sites for kainate, a **glutamate** receptor agonist, are present on mossy fibers. Here we summarize recent experiments on the role of these presynaptic kainate receptors (KARs). Application of kainate has a direct effect on the amplitude of the extracellularly recorded fiber volley, with an enhancement by low concentrations and a depression by high concentrations. These effects are mediated by KARs, because they persist in the presence of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-selective antagonist GYKI 53655, but are blocked by the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/KAR antagonist 6-cyano-7-nitroquinoxaline-2,3-dione and the KAR antagonist SYM2081. The effects on the fiber volley are most likely caused by a depolarization of the fibers via the known ionotropic actions of KARs, because application of potassium mimics the effects. In addition to these effects on fiber excitability, low concentrations of kainate enhance transmitter release, whereas high concentrations depress transmitter release. Importantly, the synaptic release of **glutamate** from mossy fibers also activates these presynaptic KARs, causing an enhancement of the fiber volley and a facilitation of release that lasts for many seconds. This positive feedback contributes to the dramatic frequency facilitation that is characteristic of mossy fiber synapses. It will be interesting to determine how widespread facilitatory presynaptic KARs are at other synapses in the central nervous system.

L84 ANSWER 15 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:562766 BIOSIS
DOCUMENT NUMBER: PREV200100562766
TITLE: Expression of functional **glutamate** transporter GLT-1 (EAAT2) in adult neurons.
AUTHOR(S): Suchak, S. K. (1); Baloyianni, N. (1); Meldrum, B. S. (1); Rattray, M. (1)
CORPORATE SOURCE: (1) Centre for Neuroscience Research, GKT Sch Biomed Sci, King's College London, London UK

SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 1873. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The five members of the Excitatory Amino Acid Transporter familiy, EAAT1 (GLAST), EAAT2 (GLT-1), EAAT3 (EAAC1), EAAT4 and EAAT5, play vital roles in recycling **glutamate** and controlling synaptic **glutamate** levels. The "glial" transporter EAAT2 accounts for 90% of total CNS **glutamate** uptake. Evidence suggests that neurons are capable of high affinity, sodium-dependent **glutamate** uptake, but the identity of the EAATs involved are unknown. Cultured neurons express several EAAT isoforms including EAAT2. In vivo, EAAT2 mRNA, but not significant levels of protein, have been detected within subsets of neurons, including cerebral cortex and hippocampal neurons. Pharmacological and biochemical approaches were employed to determine which **glutamate** transporters are functional in adult neurons and glia. Rat and mouse synaptosomes and Glial Plasmalemmal Vesicles (GPV) were prepared and uptake of 3H-l-**glutamate** or 3H-d-aspartate measured to estimate neuronal and glial uptake. Radioligand uptake was higher in GPV than synaptosomes (24pmol/mg/min v 10pmol/min/mg). A variety of drugs were used to block uptake: DHK, SYM2081 and PDC, all showing greater specificity for EAAT2 over the other EAATs; T3MG which only shows activity at EAAT2; and SOS with a 10 fold greater affinity for EAAT1 than EAAT2. GPV and synaptosomes had similar pharmacological profiles, suggesting neurons predominantly expressed EAAT2. Western blotting determined expression of EAAT1 and EAAT2 in both synaptosomes and GPVs. EAAT2 levels in the synaptosomes were 11% of GPV levels. The study indicates that the main **glutamate** transporter in nerve terminals is EAAT2.

L84 ANSWER 16 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:534323 BIOSIS
DOCUMENT NUMBER: PREV200100534323
TITLE: Antinociceptive effects of GluR5 kainate receptor agonists in normal and sensitized states: A role for gabaergic mechanisms.
AUTHOR(S): Mascias, P. (1); Herrero, J. F.; Chizh, B. A. (1)
CORPORATE SOURCE: (1) Pharmacology, Grunenthal GmbH R and D, Aachen Germany
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 1270. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB GluR5 receptors have been shown to modulate spinal nociception, however, their role in nociceptive hypersensitivity remains unclear. We have investigated the antinociception by GluR5 agonists in acute and hyperalgesic states. Moreover, as gabaergic mechanisms may be involved in the effects of GluR5 ligands in some brain structures, we queried if they play a role in spinal antinociception. The GluR5/6 agonist, SYM2081, and the GluR5 selective agonist, ATPA, were tested in vitro in spinal cord preparations from immature rats with or without peripheral carrageenan inflammation, and behaviourally on mechanical nociceptive thresholds. Both SYM2081 (100 mg/kg i.p.) and ATPA (5 mg/kg i.p.) were antihyperalgesic in behavioural tests. In vitro, ATPA (0.01-3 muM), but not SYM2081 (0.1-10

muM), dose-dependently inhibited ventral root responses to high intensity single and repetitive (1 Hz) dorsal root stimulation and the rate of cumulative depolarisation. Low intensity evoked responses were only marginally inhibited by ATPA. There was no significant difference between inflamed and non-inflamed preparations in vitro. The antinociceptive effect of ATPA (1 muM) in vitro was substantially attenuated in the presence of the GABAA antagonist bicuculline (10 muM). We conclude that GluR5 kainate receptors modulate spinal nociceptive transmission in normal and sensitized states. The antinociceptive action of GluR5 agonists may involve gabaergic mechanisms in the spinal cord. The difference between the two GluR5 agonists in vitro could be explained by their different subtype selectivity or receptor desensitization profiles.

L84 ANSWER 17 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:298613 BIOSIS
DOCUMENT NUMBER: PREV200100298613
TITLE: **Glutamate** receptor subtypes in horizontal cells in the human retina.
AUTHOR(S): Shen, W. (1); Slaughter, M. M. (1)
CORPORATE SOURCE: (1) Depts of Physiol and Biophysics, and Ophthalmology, SUNY at Buffalo, Buffalo, NY USA
SOURCE: IOVS, (March 15, 2001) Vol. 42, No. 4, pp. S509. print.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA April 29-May 04, 2001
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L84 ANSWER 18 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:87454 BIOSIS
DOCUMENT NUMBER: PREV200100087454
TITLE: Non-NMDA **glutamate** receptor mediated currents in AII amacrine cells in the rat retina.
AUTHOR(S): Morkve, S. H. (1); Hartveit, E.
CORPORATE SOURCE: (1) University of Bergen, Bergen Norway
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-248 12. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB AII amacrine cells receive the majority of their bipolar input from rod bipolar cells, with **glutamate** being the likely transmitter candidate. They express ionotropic **glutamate** receptors of both the NMDA and the non-NMDA type. Non-NMDA receptors are classified as either AMPA or kainate receptors. The lack of specificity of the agonists AMPA and kainate for their respective receptors, however, impedes the discrimination between these receptors. The question therefore arises whether the non-NMDA receptors expressed by AII amacrine cells are of the AMPA or kainate type, or both. In order to address this, we have obtained whole-cell voltage-clamp recordings (Cs-gluconate, TEA, +/- spermine) from visually identified AII amacrine cells in vertical slices of rat retina. Drugs were applied in the bath and by pressure from a multi-barrel pipette complex. Both AMPA and kainate evoked a conductance increase with current reversal close to 0 mV and the currents were blocked by CNQX. The current-voltage relationship of both AMPA and kainate displayed no rectification, independent of the presence of spermine intracellularly. From concentration-response curves for AMPA, EC50 and the Hill coefficient were calculated as apprx50 muM and 1.2. The corresponding values for

kainate were apprx75 muM and 2.0. The response to AMPA was potentiated by the drug cyclothiazide, presumably by blocking receptor desensitization. The non-competitive AMPA receptor antagonist GYKI 53655 blocked the response to both AMPA and kainate. Because kainate receptors exhibit a strongly desensitizing response to kainate, we have attempted to reveal a putative response by blocking this desensitization with concanavalin A. Treatment with conA has not revealed a response to kainate or the kainate receptor-specific agonist SYM 2081. We therefore conclude that AMPA receptors (with no Ca2+ permeability), but not kainate receptors, will be involved in mediating glutamatergic input to AII amacrine cells.

L84 ANSWER 19 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:146909 BIOSIS
DOCUMENT NUMBER: PREV200000146909
TITLE: Effects of concanavalin A on functionally expressed GluR6 detected with aequorin in a stable cell line.
AUTHOR(S): Kronbach, C. (1); Mueller, K. (1); Rosenkranz, I. (1); Kronbach, T. (1)
CORPORATE SOURCE: (1) Dept. Biochemistry, Corporate R and D ASTA Medica AG, Arzneimittelwerk Dresden, Meissner Str. 191, 01445, Radebeul Germany
SOURCE: Society for Neuroscience Abstracts., (1999) Vol. 25, No. 1-2, pp. 1489.
Meeting Info.: 29th Annual Meeting of the Society for Neuroscience. Miami Beach, Florida, USA October 23-28, 1999 Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L84 ANSWER 20 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:113898 BIOSIS
DOCUMENT NUMBER: PREV199799413101
TITLE: (2S,4R)-4-methylglutamic acid (SYM 2081): A selective, high-affinity ligand for kainate receptors.
AUTHOR(S): Zhou, L.-M.; Gu, Z.-Q.; Costa, A. M.; Yamada, K. A.; Mansson, P. E.; Giordano, T.; Skolnick, P.; Jones, K. A. (1)
CORPORATE SOURCE: (1) Synaptic Pharm. Corp., 215 College Rd., Paramus, NJ 07652 USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics, (1997) Vol. 280, No. 1, pp. 422-427.
ISSN: 0022-3565.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Glutamic acid activates ionotropic **glutamate** receptors that mediate excitatory transmission in the central nervous system. The introduction of a methyl group at position 4 of glutamic acid imparts selectivity for kainate receptors, relative to other (N-methyl-o-aspartate and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) ionotropic **glutamate** receptors. Among the stereoisomers of 4-methylglutamic acid, the potency of the (2S,4R)-isomer (SYM 2081) to inhibit (3H)kainic acid binding to both wild-type (rat forebrain) and recombinant (GluR6) kainate receptors (IC-50 values of apprx 32 and 19 nM, respectively) was comparable to that of kainic acid (IC-50 values of apprx 13 and 28 nM, respectively). SYM 2081 was apprx 800- and 200-fold less potent as an inhibitor of radioligand binding to wild-type (rat forebrain) alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and N-methyl-D-aspartate receptors, respectively. Preexposure of human embryonic kidney 293 cells stably expressing GluR6 receptors to low concentrations of SYM 2081 (30-300 nM) resulted in a reversible blockade of the rapidly desensitizing currents produced by kainate application. At

higher concentrations, SYM 2081 (EC-50 of apprx 1 mu-M) elicited kainate-like, rapidly desensitizing, inward currents. Pretreatment of recombinant GluR6 receptors with concanavalin A both abolished the effect of SYM 2081 to block kainate-induced currents and revealed nondesensitizing currents induced by SYM 2081 alone. The latter observations provide strong support for the hypothesis that SYM 2081 blocks kainate-induced currents through a process of agonist-induced desensitization. SYM 2081 also activated alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor currents in primary cultures of cerebral cortex and, consistent with data obtained by radioligand binding, was apprx 5-fold less potent than kainate (EC-50 values of 325 and 70 mu-M, respectively) in this measure. SYM 2081 is a high-affinity, selective, kainate agonist that may prove useful both as a probe to examine the physiological functions of kainate receptors and as the prototype of a novel class of therapeutic agents.

L84 ANSWER 21 OF 26 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:79116 TOXCENTER
COPYRIGHT: Copyright 2003 ACS
DOCUMENT NUMBER: CA137070878340
TITLE: Evaluation of drugs acting at **glutamate** transporters in organotypic hippocampal cultures: new evidence on substrates and blockers in excitotoxicity
AUTHOR(S): O'Shea, Ross D.; Fodera, Melissa V.; Aprico, Karina; Dehnes, Yvette; Danbolt, Niels C.; Crawford, Duncan; Beart, Philip M.
CORPORATE SOURCE: Department of Pharmacology, Monash University, Vic, 3800, Australia.
SOURCE: Neurochemical Research, (2002) Vol. 27, No. 1/2, pp. 5-13. CODEN: NEREDZ. ISSN: 0364-3190.
COUNTRY: AUSTRALIA
DOCUMENT TYPE: Journal
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2002:239944
LANGUAGE: English
ENTRY DATE: Entered STN: 20020403
Last Updated on STN: 20030506

AB Removal of L-**glutamate** (Glu) from the synapse is crit. to maintain normal transmission and to prevent excitotoxicity, and is performed exclusively by excitatory amino acid transporters (EAATs). We investigated the effects of substrates and blockers of EAATs on extracellular Glu and cellular viability in organotypic cultures of rat hippocampus. Seven-day treatment with a range of drugs (L-trans-pyrrolidine-2,4-dicarboxylate, (2S,4R)-4-methyl-**glutamate**, (.+-.)-threo-3-methylglutamate and DL-threo-.beta.-benzyloxyaspartate), in the presence of 300 .mu.M added Glu, resulted in increased extracellular Glu and a significant correlation between Glu concn. and cellular injury (as indicated by lactate dehydrogenase release). In contrast, (2S,3S,4R)-2-(carboxycyclopropyl)glycine (L-CCG-III) exerted a novel neuroprotection against this toxicity, and elevations in extracellular Glu were not toxic in the presence of this compd. Similar results were obtained following two-week treatment of cultures without added Glu. While blockade of GLT-1 alone was relatively ineffective in producing excitotoxic injury, heteroexchange of Glu by EAAT substrates may exacerbate excitotoxicity.

L84 ANSWER 22 OF 26 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:176513 TOXCENTER
COPYRIGHT: Copyright 2003 ACS
DOCUMENT NUMBER: CA131182382800
TITLE: Kainate receptors coupled to Gi/Go proteins in the rat hippocampus
AUTHOR(S): Cunha, Rodrigo A.; Malva, Joao O.; Ribeiro, J. A.

CORPORATE SOURCE: Laboratory of Neurosciences, Faculty of Medicine and Department of Chemistry and Biochemistry, Faculty of Sciences, University of Lisbon, Port..
SOURCE: Molecular Pharmacology, (1999) Vol. 56, No. 2, pp. 429-433.
CODEN: MOPMA3. ISSN: 0026-895X.
COUNTRY: PORTUGAL
DOCUMENT TYPE: Journal
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1999:508729
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20020509

AB Kainate receptors are a subtype of ionotropic **glutamate** receptors, permeable to cations and thus expected to have an excitatory depolarizing action on neurons. However, kainate receptor activation inhibits .gamma.-aminobutyric acid release in the hippocampus through activation of protein kinase C in a pertussis toxin-dependent manner, suggesting a coupling of kainate receptors to G proteins. Thus, we directly investigated the G protein coupling of kainate receptors in the rat hippocampus by using a selective kainate receptor agonist, [3H](2S,4R)-4-methylglutamate ([3H]MGA). [3H]MGA bound to a single site to hippocampal membranes with a KD value of 32 nM and a Bmax value of 1024 fmol/mg protein. This binding likely represents kainate receptors because it was displaced by domoate (Ki = 4 nM), kainate (Ki = 11 nM), and 6-cyano-7-nitroquinoxaline-2,3-dione (Ki = 1.4 .mu.M), but not by .alpha.-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (Ki >10 .mu.M), (RS)-.alpha.-methyl-4-phosphonophenylglycine (Ki >10 .mu.M), or (.+-.)-1-aminocyclopentane-trans-1,3-dicarboxylic acid (Ki >10 .mu.M). Guanylyl imidodiphosphate (30 .mu.M), which uncouples all G protein-coupled receptors, shifted to the right the satn. curve of [3H]MGA (KD = 133 nM). This effect was mimicked by pretreatment of hippocampal membranes with modifiers of Gi/Go proteins [30 .mu.M N-ethylmaleimide (KD = 98 nM) or 25 .mu.g/mL pertussis toxin (KD = 95 nM)] but not by a modifier of Gs proteins [50 .mu.g/mL cholera toxin (KD = 32 nM)]. Treatment of solubilized hippocampal membranes with pertussis toxin (25 .mu.g/mL) decreased [3H]MGA affinity (KD = 105-113 nM), which was recovered by reconstitution of these pretreated solubilized hippocampal membranes with Gi/Go proteins (KD = 41-76 nM). These results indicate that hippocampal kainate receptors are coupled to Gi/Go proteins.

L84 ANSWER 23 OF 26 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:168316 TOXCENTER
COPYRIGHT: Copyright 2003 ACS
DOCUMENT NUMBER: CA12505051027W
TITLE: Cytotoxic effects of kainate ligands on HEK cell lines expressing recombinant kainate receptors
AUTHOR(S): Carver, Jeffrey M.; Mansson, P.-Erik; Cortes-Burgos, Luz; Shu, Joanne; Zhou, Li Ming; Howe, James R.; Giordano, Tony
CORPORATE SOURCE: Symphony Pharmaceuticals, Inc., Department of Molecular Biology, Malvern, PA, 19355, USA.
SOURCE: Brain Research, (1996) Vol. 720, No. 1,2, pp. 69-74.
CODEN: BRREAP. ISSN: 0006-8993.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Journal
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1996:360038
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20020730

AB Exposure of neurons either for prolonged periods of time or to high concns. of excitatory amino acids (EAA), such as **glutamate**, results in neuronal death. Kainate also causes cell toxicity through the

glutamate receptors. However, it is unclear whether the kainate receptor itself mediates any of the toxic responses. In the present study, HEK cells expressing the GluR6 .+-. KA2 receptor subunit(s) were studied for their susceptibility to toxicity through the kainate receptor by kainate ligands. The natural ligand, **glutamate**, did not result in toxicity to the recombinant cell lines over that obsd. with the untransfected HEK cells, whereas kainate produced a 2-3-fold increase in LDH in both the HEK/GluR6 and HEK/GluR6+KA2 cell lines following treatment with various dosages, but did not affect the HEK cells. Similar 2-3-fold increases in LDH activity were detected in both recombinant cell lines following treatment with 100 nM of SYM2081 ((2S,4R)-4-methylglutamic acid), a dose at which agonistic activity is elicited. The rank order potencies for eliciting toxicity are consistent with the previously reported EC50 values (SYM2081 > kainate >>> **glutamate**). Surprisingly, the kainate antagonist, NBQX, was the most toxic of the compds. tested although it had an affinity for the kainate receptor similar to **glutamate**. Treatment with as little as 10 nM elicited a dramatic increase in toxicity (6-10-fold) in the recombinant cell lines. At 1 .mu.M, NBQX was significantly more toxic (Fisher PLSD) than any of the other compds. tested. Thus, it appears that cell toxicity can be mediated via kainate receptor through two independent mechanisms: activation and blockage of the kainate receptor.

L84 ANSWER 24 OF 26 USPATFULL
ACCESSION NUMBER: 2002:330336 USPATFULL
TITLE: Methods for modulation, stimulation, and inhibition of glutamate reuptake
INVENTOR(S): Maccecchini, Maria-Luisa, West Chester, PA, UNITED STATES
Pei, Xue-Feng, Lansdale, PA, UNITED STATES
PATENT ASSIGNEE(S): Annovis. Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002188022	A1	20021212
APPLICATION INFO.:	US 2001-21177	A1	20011030 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-244252P	20001030 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PATREA L. PABST, HOLLAND & KNIGHT LLP, SUITE 2000, ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, N.E., ATLANTA, GA, 30309-3400
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 13 Drawing Page(s
LINE COUNT: 1053
CAS INDEXING IS AVAILABLE FOR THIS PATENT
AB Disclosed is a method for inhibiting, stimulating, modulating, or regulating glutamate reuptake. The method makes use of compounds that are ligands of glutamate receptors, including many agonists, or antagonists of glutamate receptors. It has been discovered that such compounds can bind to or modulate glutamate transporters and affect extracellular glutamate levels by affecting transporter activity. The disclosed compounds can have a variety of effects on glutamate transporter activity including activation or inhibition. Such compounds are useful to treat various neurological diseases and conditions involving glutamate transporter and glutamate receptor activation. For example, excess extracellular glutamate is a cause of excessive activation of glutamate receptors. Stimulating glutamate reuptake by glutamate transporters can ameliorate excessive activation of glutamate

receptors by reducing the extracellular glutamate concentration. Prodrug forms of transporter compounds can be used as drugs.

IT **31137-74-3**, SYM 2081
(glutamate receptor ligands for modulation, stimulation, and inhibition of glutamate transport)

L84 ANSWER 25 OF 26 USPATFULL

ACCESSION NUMBER:	2002:214299 USPATFULL
TITLE:	Screen for glutamate reuptake inhibitors, stimulators, and modulators
INVENTOR(S):	Beart, Philip M., Ivanhoe, AUSTRALIA O'Shea, Ross D., Blackburn South, AUSTRALIA Aprico, Karina, Forest Hill, AUSTRALIA Lawrence, Andrew J., Brighton, AUSTRALIA Maccecchini, Maria-Luisa, West Chester, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002115688	A1	20020822
APPLICATION INFO.:	US 2001-944954	A1	20010901 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-229952P	20000901 (60)
	US 2000-230159P	20000901 (60)

dupl

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	PATREA L. PABST, HOLLAND & KNIGHT LLP, SUITE 2000, ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, N.E., ATLANTA, GA, 30309-3400
NUMBER OF CLAIMS:	27
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	14 Drawing Page(s)
LINE COUNT:	1184

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed is a method for identifying compounds that bind to or modulate a glutamate transporter. The disclosed method is useful for identifying compounds that can inhibit, stimulate, or modulate the activity of the glutamate transporter and thus affect glutamate reuptake. The method is a screening technique where compounds known to bind to glutamate receptors (for example, glutamate receptor ligands, including many agonists, and antagonists) are bound to a glutamate transporter and compounds are screened to identify those that can alter the binding of the glutamate receptor-binding compounds. Compounds shown to alter the binding of the receptor compounds from glutamate transporters in the disclosed assay can have a variety of effects on glutamate transporter activity including activation or inhibition. These compounds are expected to affect or interfere with glutamate reuptake by the glutamate transporter and thus can be used to modulate, stimulate, or inhibit glutamate reuptake. Such compounds are useful to treat various neurological diseases and conditions involving glutamate transporter and glutamate receptor activation. One of the compounds is (2S,4R)-4-methylglutamate or [.sup.3H]-(2S,4R)-4-methylglutamate. For example, excess extracellular glutamate is a cause of excessive activation of glutamate receptors. Stimulating glutamate reuptake by glutamate transporters can ameliorate excessive activation of glutamate receptors by reducing the extracellular glutamate concentration. Prodrug forms of transporter compounds are preferred for use as drugs.

IT **31137-74-3**
(screening for glutamate reuptake inhibitors, stimulators, and modulators)

L84 ANSWER 26 OF 26 USPATFULL

ACCESSION NUMBER:	1998:31053 USPATFULL
TITLE:	Alkylcarboxy amino acids-modulators of the kainate receptor
INVENTOR(S):	Gu, Zi-Qiang, Rosemont, PA, United States
PATENT ASSIGNEE(S):	Bearsden Bio, Inc., Philadelphia, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5731348		19980324
APPLICATION INFO.:	US 1996-600330		19960213 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1995-389916, filed on 15 Feb 1995, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Jarvis, William R. A.		
LEGAL REPRESENTATIVE:	Arnall, Golden & Gregory, LLP		
NUMBER OF CLAIMS:	6		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	4 Drawing Figure(s); 3 Drawing Page(s)		
LINE COUNT:	1243		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds of a new class of alkyl carboxy amino acid analogs of glutamic acid act as specific regulators of the kainic acid EAA receptor cation channel. These compounds are useful for treating neurological, neuropsychological, neuropsychiatric, neurodegenerative, neuropsychopharmacological and functional disorders associated with excessive or insufficient activation of the kainic acid subtype of the ionotropic EAA receptors; treating cognitive disorders associated with deactivation, suboptimal activation or over-activation of the kainic acid receptor; alleviating pain and improving and enhancing memory, learning, and associated mental processes. A method for designing novel AMPA or kainic acid receptor agonists or antagonists is also disclosed.

IT **31137-74-3P**
(prepn. of carboxyalkyl amino acids as modulators of the kainate receptor)

FILE 'HOME' ENTERED AT 12:22:54 ON 25 JUN 2003

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=> fil medl drugu embase wpids scisearch
FILE 'MEDLINE' ENTERED AT 12:03:30 ON 25 JUN 2003

FILE 'DRUGU' ENTERED AT 12:03:30 ON 25 JUN 2003
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FILE 'EMBASE' ENTERED AT 12:03:30 ON 25 JUN 2003
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FILE 'SCISEARCH' ENTERED AT 12:03:30 ON 25 JUN 2003
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=> d que l75; d que l80; s l75 or l80
L68           74 SEA SYM(W)(2081 OR 2083 OR 2062 OR 2051)
L69           12 SEA SYM2081 OR SYM2083 OR SYM2062 OR SYM2051
L70            1 SEA LY310214 OR LY 310214
L71            9 SEA ERYTHRO(2A)(METHYLGLUTAM? OR METHYL(2A) GLUTAM?)
L72       206656 SEA GLUTAMATE OR GLUTAMIC ACID
L73       508158 SEA UPTAK? OR REUPTAK?
L74         6921 SEA L72(3A) LEVEL#
L75            4 SEA (L68 OR L69 OR L70 OR L71) AND ((L72 AND L73) OR L74)



L68           74 SEA SYM(W)(2081 OR 2083 OR 2062 OR 2051)
L69           12 SEA SYM2081 OR SYM2083 OR SYM2062 OR SYM2051
L70            1 SEA LY310214 OR LY 310214
L71            9 SEA ERYTHRO(2A)(METHYLGLUTAM? OR METHYL(2A) GLUTAM?)
L72       206656 SEA GLUTAMATE OR GLUTAMIC ACID
L76           70 SEA (L68 OR L69 OR L70 OR L71) AND L72
L77      3096538 SEA BRAIN OR NERVE# OR NEURON? OR NERVOUS SYSTEM
L79       228690 SEA L77(5A)(DISEASE# OR DISORDER# OR DYSFUNCTION?)
L80            4 SEA L76 AND L79



L81            8 L75 OR L80

=> dup rem l81
PROCESSING COMPLETED FOR L81
L82            4 DUP REM L81 (4 DUPLICATES REMOVED)
                 ANSWERS '1-2' FROM FILE MEDLINE
                 ANSWER '3' FROM FILE DRUGU
                 ANSWER '4' FROM FILE EMBASE

=> d iall 1-4; fil hom

L82  ANSWER 1 OF 4     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:    1998260314     MEDLINE
DOCUMENT NUMBER:     98260314   PubMed ID: 9580595
TITLE:               The methylglutamate, SYM 2081, is a
                     potent and highly selective agonist at kainate receptors.
AUTHOR:              Donevan S D; Beg A; Gunther J M; Twyman R E
CORPORATE SOURCE:    Department of Neurology, University of Utah, Salt Lake
                     City, USA.
CONTRACT NUMBER:     NS31519 (NINDS)
SOURCE:              JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS,
                     (1998 May) 285 (2) 539-45.
                     Journal code: 0376362. ISSN: 0022-3565.
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text search

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980618
Last Updated on STN: 19980618
Entered Medline: 19980608

ABSTRACT:
The methylglutamate analog (2S,4R)-4-methylglutamate (**SYM** ***2081***) has been shown to potently displace high affinity [3H]kainate binding to cortical tissue and to recombinant kainate receptors, and to evoke rapidly desensitizing responses in electrophysiological recordings. We have used two electrode voltage clamp recordings to compare the potency and efficacy of **SYM 2081** with other alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA)/kainate receptor agonists at homomeric kainate and AMPA receptors expressed in Xenopus oocytes. In the presence of concanavalin A to reduce agonist induced desensitization at kainate receptors, **SYM** ***2081*** was a potent agonist at homomeric kainate receptors composed of the GluR5 and GluR6 subunit, with an EC50 of 0.12 +/- 0.02 and 0.23 +/- 0.01 microM, respectively. **SYM 2081** was highly selective for kainate receptors, the EC50 for activation of AMPA receptors composed of the GluR1 and GluR3 subunits was 132 +/- 44 and 453 +/- 57 microM, respectively. Other methylglutamate analogs were tested for kainate receptor agonist activity. Methylglutamate compounds with the methyl group at the 2 or 3 position of **glutamate** were inactive indicating that positioning of the methyl group at the 4 position was essential for agonist activity. Of the four stereoisomers of 4-methylglutamate, **SYM 2081** (2S,4R) was the most potent agonist. The (2R,4R) isomer was estimated to be 20-fold and the (2S,4S)-isomer approximately 1000-fold less potent than **SYM** ***2081*** . These results indicate that **SYM 2081** is a potent and selective agonist at kainate receptors, and thus will be a useful ligand for evaluating the role of kainate receptors in central **nervous** ***system*** function and **disease**.

CONTROLLED TERM: Check Tags: Animal; Female; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Glutamates: PD, pharmacology
Receptors, AMPA: DE, drug effects
*Receptors, Kainic Acid: AG, agonists
Receptors, Kainic Acid: PH, physiology
Stereoisomerism
Structure-Activity Relationship
Xenopus
CAS REGISTRY NO.: 14561-55-8 (4-methylglutamic acid)
CHEMICAL NAME: 0 (Glutamates); 0 (Receptors, AMPA); 0 (Receptors, Kainic Acid)

L82 ANSWER 2 OF 4 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 93218798 MEDLINE
DOCUMENT NUMBER: 93218798 PubMed ID: 8096630
TITLE: **Glutamate uptake** system in the presynaptic vesicle: **glutamic acid** analogs as inhibitors and alternate substrates.
AUTHOR: Winter H C; Ueda T
CORPORATE SOURCE: Department of Biological Chemistry, Medical School, University of Michigan, Ann Arbor 48109.
CONTRACT NUMBER: NS 026107 (NINDS)
SOURCE: NEUROCHEMICAL RESEARCH, (1993 Jan) 18 (1) 79-85.
Journal code: 7613461. ISSN: 0364-3190.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199305
ENTRY DATE: Entered STN: 19930521
Last Updated on STN: 20000303
Entered Medline: 19930506

ABSTRACT:
A variety of naturally occurring amino acids, their isomers, and synthetic analogs were tested for their ability to inhibit **uptake** of [3H] ***glutamate*** into presynaptic vesicles from bovine cerebral cortex. Strongest inhibition (Ki < 1mM) was observed for trans-1-aminocyclopentane-1,3-dicarboxylic acid (t-ACPD) and **erythro-4-methyl-L-** ***glutamic*** **acid** (MGlu), while 4-methylene-L-**glutamic** ***acid*** (MeGlu) was only moderately inhibitory (Ki = approximately 3mM), indicating that the synaptic vesicle **glutamate** translocator has higher affinity for trans-ACPD and MGlu than for **glutamate**. A few other amino acids, e.g., 4-hydroxyglutamic acid, S-carboxyethyl cysteine, and 5-fluorotryptophan, were slightly inhibitory; all L- and DL-isomers of protein amino acids and longer chain acidic amino acids were without measurable inhibition. Potassium tetrathionate and S-sulfocysteine exhibited strong to moderate noncompetitive or irreversible inhibition. Inhibition by t-ACPD, MGlu, or MeGlu was competitive with **glutamic acid**. Each of these competitive inhibitors was also taken up by the vesicle preparation in an ATP-dependent manner, as indicated by their being recovered unchanged from filtered vesicles. Similar results were obtained with reconstituted vesicles, while **glutamate uptake** by partially purified rat synaptosomes was inhibited only by MGlu. These results indicate that the ***glutamate*** translocator of presynaptic vesicles has stringent structural requirements distinct from those of the plasma membrane translocator and the metabotropic type of postsynaptic **glutamate** receptor. They further suggest possible structural requirements of pharmacologically significant compounds that can substitute for **glutamic acid** in the presynaptic side of glutamatergic synapses, thus serving to moderate or control ***glutamate*** excitation and associated excitotoxic effects in these neurons.

CONTROLLED TERM: Check Tags: Animal; Support, U.S. Gov't, P.H.S.
Cattle
*Cerebral Cortex: ME, metabolism
Cycloleucine: AA, analogs & derivatives
Cycloleucine: ME, metabolism
Cycloleucine: PD, pharmacology
Cysteine: AA, analogs & derivatives
Cysteine: PD, pharmacology
*Glutamates: ME, metabolism
*Glutamates: PD, pharmacology
Glutamic Acid
Synaptic Vesicles: DE, drug effects
*Synaptic Vesicles: ME, metabolism
Tryptophan: AA, analogs & derivatives
Tryptophan: PD, pharmacology

CAS REGISTRY NO.: 111900-32-4 (1-amino-1,3-dicarboxycyclopentane); 14561-55-8 (4-methylglutamic acid); 1637-71-4 (S-sulphocysteine); 343-91-9 (5-fluorotryptophan); 52-52-8 (Cycloleucine); 52-90-4 (Cysteine); **56-86-0 (Glutamic Acid)**; 7150-74-5 (4-methyleneglutamic acid); 73-22-3 (Tryptophan)

CHEMICAL NAME: 0 (Glutamates)

L82 ANSWER 3 OF 4 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1998-12102 DRUGU P
TITLE: A novel kainate receptor ligand (3H)-(2S,4R)-4-methylglutamate: pharmacological characterization in rabbit brain membranes.
AUTHOR: Toms N J; Reid M E; Phillips W; Kemp M C; Roberts P J
CORPORATE SOURCE: Univ.Bristol; Tocris-Cookson
LOCATION: Bristol, U.K.

SOURCE: Neuropharmacology (36, No. 11-12, 1483-88, 1997) 4 Fig. 1 Tab. 21 Ref.
CODEN: NEPHBW ISSN: 0028-3908
AVAIL. OF DOC.: Department of Pharmacology, School of Medical Sciences, University of Bristol, University Walk, Bristol BS8 1TD, England. (email: P.J.Roberts@bristol.ac.uk). (P.J.R.).
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

In rabbit whole brain membranes in-vitro, 3H-(2S,4R)-4-methylglutamate (MG, ***SYM*** **-2081**) bound to 2 sites. Characterization with antagonists indicated that MG was a useful ligand for labelling kainate receptors, with high selectivity and a pharmacology similar to that for rat cloned low affinity (Glu5 and 6) kainate receptor subunits.

SECTION HEADING: P Pharmacology

CLASSIF. CODE: 60 Autonomic
63 Receptors
73 Trial Preparations

CONTROLLED TERM:
[01] **SYM-2081** *PH; KAINATE *RC; **GLUTAMATE** *RC; DOMOATE *RC; QUISQUALATE *RC; FG-9065 *RC; AMPA *RC; FLUOROWILLARDIINE *RC; METHYLASPARTATE-N *RC; NS-102 *RC; AMINOPHOSPHONOBUTANOATE *RC; DR9505061 *RN; IN-VITRO *FT; RABBIT *FT; BRAIN *FT; MEMBRANE *FT; KAINATE-RECEPTOR *FT; BINDING *FT; CHARACTERIZATION *FT; TRITIUM-LABELED *FT; AFFINITY *FT; LAB.ANIMAL *FT; SUBCELL.STRUCT. *FT; RECEPTOR *FT; **GLUTAMATE** -RECEPTOR *FT; TRIAL-PREP. *FT; PH *FT
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L82 ANSWER 4 OF 4 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999049700 EMBASE
TITLE: Society for Neuroscience - 28th Annual Meeting: **Glutamate** receptors.
AUTHOR: Salt T.
CORPORATE SOURCE: T. Salt, Department of Visual Science, Institute of Ophthalmology, University College London, 11-43 Bath Street, London EC1V 9EL, United Kingdom. T.SALT@UCLAC.UK
SOURCE: IDrugs, (1999) 2/1 (1-3).
ISSN: 1369-7056 CODEN: IDRUFN
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
This meeting, stretching over 5 days with approximately 24,000 registrants, had approximately 13,000 oral and poster presentations covering all areas of neuroscience. This review focuses on a selection of new developments in the field of **glutamate** receptors. This area is receiving considerable attention from research groups in both academic and industrial establishments, and it is notable that many efforts are collaborative between workers from these different types of establishment. **Glutamate** receptors (GluR) can be classified as ionotropic (iGluR) or metabotropic (mGluR) receptors. Amongst the ionotropic receptors are the NMDA receptors, AMPA receptors and

kainate receptors, whilst there are eight subtypes of mGluRs which can be placed into three groups on the basis of sequence homology, pharmacology and intracellular transduction mechanism.

CONTROLLED TERM: Medical Descriptors:
***brain disease**
*drug mechanism
brain protection
epilepsy
analgesia
nerve degeneration
protein domain
brain infarction
cognitive defect
neurotoxicity
human
nonhuman
mouse
animal experiment
controlled study
human cell
animal cell
conference paper
Drug Descriptors:
***glutamate receptor**
*ionotropic receptor
*cp 465022: DV, drug development
*2 (3 carboxybicyclo[1.1.1]pentyl)glycine: DV, drug development
*rpr 118723: DV, drug development
*ly 393675: DV, drug development
quisqualic acid receptor
n methyl dextro aspartic acid receptor
kainic acid receptor
1 (4 aminophenyl) 3,4 dihydro 4 methyl 3 methylcarbamoyl 7,8 methylenedioxy 5h 2,3 benzodiazepine
decahydro 6 [2 (1h tetrazol 5 yl)ethyl] 3 isoquinolinecarboxylic acid
4 methylglutamic acid
ly 379268: DV, drug development
glutamate receptor agonist: DV, drug development
AMPA receptor antagonist: DV, drug development
glutamic acid antagonist: DV, drug development
cgp 68730a: DV, drug development
upf 596

CAS REGISTRY NO.: (1 (4 aminophenyl) 3,4 dihydro 4 methyl 3 methylcarbamoyl 7,8 methylenedioxy 5h 2,3 benzodiazepine) 143692-48-2; (decahydro 6 [2 (1h tetrazol 5 yl)ethyl] 3 isoquinolinecarboxylic acid) 154652-83-2; (4 methylglutamic acid) 14561-55-8

CHEMICAL NAME: (1) Ly 293558; (2) Gyki 53655; **(3) Sym 2081**; (4) Ly 393675; (5) Cp 465022; (6) Rpr 118723; (7) Ly 379268; (8) Cgp 68730a; Upf 596

COMPANY NAME: (2) Egis gyogyszergyar; (3) Symphony; (5) Pfizer; (6) Rhone Poulenc Rorer; (7) Lilly; (8) Novartis

FILE 'HOME' ENTERED AT 12:03:58 ON 25 JUN 2003

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l37
FILE 'CAPLUS' ENTERED AT 11:51:33 ON 25 JUN 2003
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FILE COVERS 1907 - 25 Jun 2003  VOL 138 ISS 26
FILE LAST UPDATED: 24 Jun 2003  (20030624/ED)
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inventor search

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  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


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L2           257 SEA FILE=CAPLUS ABB=ON  PEI X?/AU
L3             7 SEA FILE=CAPLUS ABB=ON  L1 AND L2


L1            41 SEA FILE=CAPLUS ABB=ON  MACCECCHINI M?/AU
L2           257 SEA FILE=CAPLUS ABB=ON  PEI X?/AU
L5         11863 SEA FILE=CAPLUS ABB=ON  GLUTAMATE RECEPTORS/CT
L8        256906 SEA FILE=CAPLUS ABB=ON  ?UPTAKE?
L9             1 SEA FILE=CAPLUS ABB=ON  (L1 OR L2) AND L5 AND L8


L50            7 L3 OR L9

FILE 'BIOSIS' ENTERED AT 11:51:33 ON 25 JUN 2003
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 19 June 2003 (20030619/ED)


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L34          144 SEA FILE=BIOSIS ABB=ON  PEI X?/AU
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L31        72397 SEA FILE=BIOSIS ABB=ON  GLUTAMATE#
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L34          144 SEA FILE=BIOSIS ABB=ON  PEI X?/AU
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L51            7 L36 OR L37

=> fil toxcenter; d que 143; d que 146; d que 148; s 143 or 146 or 148
FILE 'TOXCENTER' ENTERED AT 11:51:54 ON 25 JUN 2003
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FILE COVERS 1907 TO 24 Jun 2003 (20030624/ED)

This file contains CAS Registry Numbers for easy and accurate substance
identification.

TOXCENTER has been enhanced with new files segments and search fields.
See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the
MeSH 2003 vocabulary.  See http://www.nlm.nih.gov/mesh/summ2003.html
for a description on changes.


L41           17 SEA FILE=TOXCENTER ABB=ON  MACCECCHINI M?/AU
L42           83 SEA FILE=TOXCENTER ABB=ON  PEI X?/AU
L43            1 SEA FILE=TOXCENTER ABB=ON  L41 AND L42



L39        39154 SEA FILE=TOXCENTER ABB=ON  GLUTAMATE#
L41           17 SEA FILE=TOXCENTER ABB=ON  MACCECCHINI M?/AU
L42           83 SEA FILE=TOXCENTER ABB=ON  PEI X?/AU
L45       117819 SEA FILE=TOXCENTER ABB=ON  REUPTAK? OR UPTAK?
L46            1 SEA FILE=TOXCENTER ABB=ON  (L41 OR L42) AND L39 AND L45



L39        39154 SEA FILE=TOXCENTER ABB=ON  GLUTAMATE#
L41           17 SEA FILE=TOXCENTER ABB=ON  MACCECCHINI M?/AU
L42           83 SEA FILE=TOXCENTER ABB=ON  PEI X?/AU
L47         1877 SEA FILE=TOXCENTER ABB=ON  L39(3A)LEVEL#
L48            1 SEA FILE=TOXCENTER ABB=ON  L47 AND (L41 OR L42)



L52            1 L43 OR L46 OR L48

=> fil medl; d que l55;d que l57
FILE 'MEDLINE' ENTERED AT 11:57:01 ON 25 JUN 2003

 FILE LAST UPDATED: 24 JUN 2003 (20030624/UP).  FILE COVERS 1958 TO DATE.

 On April 13, 2003, MEDLINE was reloaded.  See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2003 vocabulary.  See http://www.nlm.nih.gov/mesh/changes2003.html
 for a description on changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
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L54         135 SEA FILE=MEDLINE ABB=ON  PEI X?/AU
L55           1 SEA FILE=MEDLINE ABB=ON  L53 AND L54



L53          16 SEA FILE=MEDLINE ABB=ON  MACCECCHINI M?/AU
L54         135 SEA FILE=MEDLINE ABB=ON  PEI X?/AU
L56       16750 SEA FILE=MEDLINE ABB=ON  GLUTAMIC ACID/CT
L57           2 SEA FILE=MEDLINE ABB=ON  (L53 OR L54) AND L56


=> s l55 or l57
L65           3 L55 OR L57

=> fil embase; d que l60; d que l64; s l60 or l64
FILE 'EMBASE' ENTERED AT 11:57:25 ON 25 JUN 2003
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 FILE COVERS 1974 TO 19 Jun 2003 (20030619/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

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 substance identification.


L58          13 SEA FILE=EMBASE ABB=ON  MACCECCHINI M?/AU
L59          89 SEA FILE=EMBASE ABB=ON  PEI X?/AU
L60           1 SEA FILE=EMBASE ABB=ON  L58 AND L59



L58          13 SEA FILE=EMBASE ABB=ON  MACCECCHINI M?/AU
L59          89 SEA FILE=EMBASE ABB=ON  PEI X?/AU
L61       27232 SEA FILE=EMBASE ABB=ON  GLUTAMIC ACID/CT
L62           2 SEA FILE=EMBASE ABB=ON  GLUTAMATE UPTAKE INHIBITOR/CT
L64           2 SEA FILE=EMBASE ABB=ON  (L58 OR L59) AND (L61 OR L62)



L66           3 L60 OR L64

=> dup rem l65,l50,l51,l66,l52
FILE 'MEDLINE' ENTERED AT 11:57:37 ON 25 JUN 2003

FILE 'CAPLUS' ENTERED AT 11:57:37 ON 25 JUN 2003
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PROCESSING COMPLETED FOR L65
PROCESSING COMPLETED FOR L50
PROCESSING COMPLETED FOR L51
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PROCESSING COMPLETED FOR L66
PROCESSING COMPLETED FOR L52
L67 13 DUP REM L65 L50 L51 L66 L52 (8 DUPLICATES REMOVED)
ANSWERS '1-3' FROM FILE MEDLINE
ANSWERS '4-9' FROM FILE CAPLUS
ANSWERS '10-13' FROM FILE BIOSIS

=> d ibib ab 1-13

L67 ANSWER 1 OF 13 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001563541 MEDLINE
DOCUMENT NUMBER: 21521563 PubMed ID: 11640930
TITLE: Point mutations identify the glutamate binding pocket of the N-methyl-D-aspartate receptor as major site of conantokin-G inhibition.
AUTHOR: Wittekindt B; Malany S; Schemm R; Otvos L; **Maccecchini M L**; Laube B; Betz H
CORPORATE SOURCE: Department of Neurochemistry, Max-Planck-Institute for Brain Research, Deutschordenstrasse 46, 60528, Frankfurt/Main, Germany.
SOURCE: NEUROPHARMACOLOGY, (2001 Nov) 41 (6) 753-61.
Journal code: 0236217. ISSN: 0028-3908.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011022
Last Updated on STN: 20020125
Entered Medline: 20020110

AB Conantokin-G (Con-G), a gamma-carboxylglutamate (Gla) containing peptide derived from the venom of the marine cone snail Conus geographus, acts as a selective and potent inhibitor of N-methyl-D-aspartate (NMDA) receptors. Here, the effect of Con-G on recombinant NMDA receptors carrying point mutations within the glycine and glutamate binding pockets of the NR1 and NR2B subunits was studied using whole-cell voltage-clamp recording from cRNA injected Xenopus oocytes. At wild-type receptors, glutamate-induced currents were inhibited by Con-G in a dose-dependent manner at concentrations of 0.1-100 microM. Substitution of selected residues within the NR2B subunit reduced the inhibitory potency of Con-G, whereas similar mutations in the NR1 subunit had little effect. These results indicate a selective interaction of Con-G with the glutamate binding pocket of the NMDA receptor. Homology-based molecular modeling of the glutamate binding region based on the known structure of the glutamate binding site of the AMPA receptor protein GluR2 suggests how selected amino acid side chains of NR2B might interact with specific residues of Con-G.

L67 ANSWER 2 OF 13 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1999196294 MEDLINE
DOCUMENT NUMBER: 99196294 PubMed ID: 10098658
TITLE: Allosteric modulators of the AMPA receptor: novel 6-substituted dihydrophthalazines.
AUTHOR: **Pei X F**; Sturgess M A; Valenzuela C F; **Maccecchini M L**
CORPORATE SOURCE: Bearsden Bio, Inc., Aston, PA 19014, USA.
SOURCE: BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, (1999 Feb 22) 9 (4) 539-42.
Journal code: 9107377. ISSN: 0960-894X.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990607
Last Updated on STN: 19990607
Entered Medline: 19990524

AB Novel analogs of the allosteric AMPA receptor modulator SYM 2206 have been prepared. Structure/activity correlations of these novel analogs and other dihydrophthalazines (DHPs) reveal the important contribution of the heteroatom-based aryl substituents in this class of noncompetitive inhibitors. One of the analogs (6, SYM 2189) is equipotent with the early series, but with reduced sedation.

L67 ANSWER 3 OF 13 MEDLINE
ACCESSION NUMBER: 2000270252 MEDLINE
DOCUMENT NUMBER: 20270252 PubMed ID: 10809774
TITLE: The conformational activation of antithrombin. A 2.85-A structure of a fluorescein derivative reveals an electrostatic link between the hinge and heparin binding regions.
AUTHOR: Huntington J A; McCoy A; Belzar K J; **Pei X Y**; Gettins P G; Carrell R W
CORPORATE SOURCE: University of Cambridge, Department of Haematology, Wellcome Trust Centre for the Study of Molecular Mechanisms in Disease, Cambridge Institute for Medical Research, Hills Road, Cambridge CB2 2XY, United Kingdom.. jah52@cam.ac.uk
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 May 19) 275 (20) 15377-83.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1DZG; PDB-1DZH
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000621

AB Antithrombin is unique among the serpins in that it circulates in a native conformation that is kinetically inactive toward its target proteinase, factor Xa. Activation occurs upon binding of a specific pentasaccharide sequence found in heparin that results in a rearrangement of the reactive center loop removing constraints on the active center P1 residue. We determined the crystal structure of an activated antithrombin variant, N135Q S380C-fluorescein (P14-fluorescein), in order to see how full activation is achieved in the absence of heparin and how the structural effects of the substitution in the hinge region are translated to the heparin binding region. The crystal structure resembles native antithrombin except in the hinge and heparin binding regions. The absence of global conformational change allows for identification of specific interactions, centered on Glu(381) (P13), that are responsible for maintenance of the solution equilibrium between the native and activated forms and establishes the existence of an electrostatic link between the hinge region and the heparin binding region. A revised model for the mechanism of the allosteric activation of antithrombin is proposed.

L67 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
ACCESSION NUMBER: 2002:391517 CAPLUS
DOCUMENT NUMBER: 136:395975
TITLE: Glutamate receptor ligands for modulation, stimulation, and inhibition of glutamate transport
INVENTOR(S): **Maccecchini, Maria-Luisa; Pei, Xue-Feng**
PATENT ASSIGNEE(S): Annovis, Inc., USA
SOURCE: PCT Int. Appl., 48 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002040002	A2	20020523	WO 2001-US48448	20011030
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002037717	A5	20020527	AU 2002-37717	20011030
US 2002188022	A1	20021212	US 2001-21177	20011030

PRIORITY APPLN. INFO.: US 2000-244252P P 20001030
WO 2001-US48448 W 20011030
OTHER SOURCE(S): MARPAT 136:395975

AB The invention discloses the use of glutamate receptor ligands (agonists and antagonists) for inhibiting, stimulating, modulating, or regulating glutamate **reuptake**. It has been discovered that such compds. can bind to or modulate glutamate transporters and affect extracellular glutamate levels by affecting transporter activity. The disclosed compds. can have a variety of effects on glutamate transporter activity including activation or inhibition. Such compds. are useful to treat various neurol. diseases and conditions involving glutamate transporter and glutamate receptor activation. For example, excess extracellular glutamate is a cause of excessive activation of glutamate receptors. Stimulating glutamate **reuptake** by glutamate transporters can ameliorate excessive activation of glutamate receptors by reducing the extracellular glutamate concn. Prodrug forms of transporter compds. can be used as drugs.

L67 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 3
ACCESSION NUMBER: 2001:640039 CAPLUS
TITLE: Novel 5H-2,3-benzodiazepine antagonists of AMPA receptors
AUTHOR(S): **Pei, Xue-Feng**; Li, Baoqing; **Maccecchini, Maria**
CORPORATE SOURCE: Department of Medicinal Chemistry, Annovis, Inc, Aston, PA, 19014, USA
SOURCE: Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, United States, August 26-30, 2001 (2001), MEDI-220. American Chemical Society: Washington, D. C.
CODEN: 69BUZP
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

AB Excitatory neuronal transmission within the central nervous system is mediated predominately by ion flux through ion channels gated by glutamate. There are three major glutamate receptor subtypes: the N-methyl-D-aspartate (NMDA), 2S-amino-2-(5'-methyl-3'-hydroxyisoxazoline)-propionic acid (AMPA), and kainic acid (KA) receptor. Compds. that inhibit AMPA receptors have been shown to be effective neutroprotectants and have potential to treat epilepsy. We disclosed a series of dihydrophthalazine (1-3) as noncompetitive AMPA receptor antagonists (J. Med. Chem. 1996, 39, 343 and Bioorg. Med. Chem. Lett., 1999, 9, 539). It was also found that GYKI 53655 (4), a 5H-2,3-benzodiazepine, is a

noncompetitive AMPA receptor antagonist. We now report synthesis of novel 5H-2,3-benzodiazepines (5-8), and their anticonvulsant activities.

L67 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:539642 CAPLUS
DOCUMENT NUMBER: 137:94003
TITLE: Preparation of esters of carbalkoxy amino acids as prodrugs of modulators of the kainate receptor
INVENTOR(S): **Pei, Xue-Feng; Maccecchini, Maria-Luisa**
PATENT ASSIGNEE(S): Annovis, Inc., USA
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002055479	A2	20020718	WO 2001-US48579	20011030
WO 2002055479	A3	20021024		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002115721	A1	20020822	US 2001-20842	20011030

PRIORITY APPLN. INFO.: US 2000-244411P P 20001030
OTHER SOURCE(S): MARPAT 137:94003
AB Title compds. R5O2CCR1R2CH2CH(NR3R4)CO2R6 [R1, R2, R5, R6 = C1-C6-alkyl, C3-C4-alkenyl, C3-C5-cycloalkyl; R3, R4 = H, any group given for R1, C1-C6-alkyl-CO, C1-C6-alkyl-O2C or -NHCO, HCO, or C3-C6-alkynyl; R3 and R4 taken together can be CH2(CH2)nCH2, where n = 0-3] or their pharmaceutically acceptable salts were prepd. as specific regulators of the kainate excitatory amino acid receptor cation channel. These compds. are useful for treating neurol. and cognitive disorders, alleviating pain, and improving and enhancing mental processes. Thus, (2S,4R)-4-methylglutamic acid di-Me ester, prepd. by esterification of the acid, prevented hyperalgesia in the rat at 10 mg/kg.

L67 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:935585 CAPLUS
DOCUMENT NUMBER: 136:69827
TITLE: Preparation of 7- or 8-mono-substituted 5H-2,3-benzodiazepines as antagonists of excitatory amino acid receptors
INVENTOR(S): **Pei, Xue-Feng**; Li, Baoqing; **Maccecchini, Maria-Luisa**
PATENT ASSIGNEE(S): Annovis, Inc., USA
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2001098280 A2 20011227 WO 2001-US19136 20010615
WO 2001098280 A3 20020530
W: CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR
US 2002025958 A1 20020228 US 2001-882843 20010615
EP 1296960 A2 20030402 EP 2001-948367 20010615
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRIORITY APPLN. INFO.: US 2000-212238P P 20000616
WO 2001-US19136 W 20010615
OTHER SOURCE(S): MARPAT 136:69827
AB Title compds. [I; dotted bond = single, double; X = N, NR; R = COCH3, CONHCH3, CONHCH2CH3, CONHCH2CH2CH3, CONHCH2CH2CH2CH3; R2 = H, OCH3, NH2, SCH3; R3 = OCH3, H, NH2, SCH3] and pharmaceutically acceptable salts are prepd. as active non-NMDA inotropic excitatory amino acid (EAA) receptor antagonists and are useful for treating disorders assocd. with excessive activation of the non-NMDA subtype of the inotropic EAA receptor. Title compds. I further are useful as testing agents to identify and characterize other compds. for the treatment of these disorders. The compds. are useful therapeutically as sedatives or for the treatment of neurosychopharmacol. disorders such as stroke, ischemia and epilepsy. The compns. may be provided in combination with a suitable carrier for oral or parenteral administration. The compds. may be administered orally or parenterally for the treatment of a variety of disorders assocd. with non-NMDA EAA receptor function.

L67 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:780863 CAPLUS
DOCUMENT NUMBER: 135:318511
TITLE: Preparation of aminophenylphthalazines as non-NMDA ionotropic excitatory amino acid receptor antagonists.
INVENTOR(S): **Pei, Xue-Feng**; Li, Baoqing; **Maccecchini, Maria-Luisa**
PATENT ASSIGNEE(S): ANNOVIS, Inc., USA
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001079181	A2	20011025	WO 2001-US11948	20010412
WO 2001079181	A3	20020321		
W: JP, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
US 2002006925	A1	20020117	US 2001-833855	20010412
EP 1274689	A2	20030115	EP 2001-969042	20010412
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				

PRIORITY APPLN. INFO.: US 2000-196823P P 20000413
WO 2001-US11948 W 20010412
OTHER SOURCE(S): MARPAT 135:318511
AB Title compds. [I; R1-R4 = H, OH, R11O, halo, alkyl, CF3, R12CO2, R12CO, R12CONH, etc.; R1R2, R2R3, R3R4 = SCH2S, SCH2O, OCH2CH2S, etc.; R5, R6 = H, alkyl, alkenyl, cycloalkyl, (substituted) Ph; R5R6 = cycloalkyl; R7 = H, alkyl, alkenyl, cycloalkyl, R13R14NCO, R13R14NCS, etc.; R6R7 = (CH2)mCHR13NCO, (CH2)mCH2O2C, etc.; R8, R9 = H, R13R14N, R12CONH, etc.; R10 = H, halo, OH, R11O, R13R14N, alkyl, CF3, R12CO2, etc.; R12 = H, alkyl; R13, R14 = H, alkyl, perfluoroalkyl, alkenyl, cycloalkyl; R13R14 =

cycloalkyl; m = 0-2], were prepd. as kainate and/or AMPA antagonists (no data). Thus, 4-(4-acetylaminophenyl)-1,2-dihydro-1-methyl-6-methylthiophthalazine in CHCl3 was treated with EtNCO to give 50% 4-(4-acetylaminophenyl)-1,2-dihydro-1-methyl-2-ethylcarbamoyl-6-methylthiophthalazine.

L67 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:796211 CAPLUS
TITLE: Novel sulfur containing dihydrophthalazine antagonists of AMPA receptors
AUTHOR(S): Li, Baoqing; **Pei, Xue-Feng; Maccecchini, Maria**
CORPORATE SOURCE: Department of Medicinal Chemistry, Annovis, Inc, Aston, PA, 19014, USA
SOURCE: Abstracts of Papers - American Chemical Society (2000), 220th, MEDI-212
CODEN: ACSRAL; ISSN: 0065-7727
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; Meeting Abstract
LANGUAGE: English
AB Excitatory neuronal transmission within the central nervous system is mediated predominately by ion flux through ion channels gated by glutamate. There are three major glutamate receptor subtypes: the N-methyl-D-aspartate (NMDA), 2S-amino-3-(5'-methyl-3'-hydroxyisoxazoline)-propionic acid (AMPA), and kainic acid (KA) receptor. Compds. that inhibit AMPA receptors have been shown to be effective neuroprotectants and have potential to treat epilepsy. We disclosed a series of promising dihydrophthalazines (DHP's) as non-competitive AMPA antagonists. We now report synthesis of novel sulfur contg. DHP's analogs. Structure-activity correlation of these novel analogs and other DHP's reveal the important contribution of the sulfur-based substituents in this class of noncompetitive inhibitors.

L67 ANSWER 10 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5
ACCESSION NUMBER: 1993:5264 BIOSIS
DOCUMENT NUMBER: PREV199395005264
TITLE: Noncompetitive inhibition of N-methyl-D-aspartate by conantokin G: Evidence for an allosteric interaction at polyamine sites.
AUTHOR(S): Skolnick, Phil (1); Boje, Kathleen; Miller, Rachel; Pennington, Micheal; **Maccecchini, Maria-Luisa**
CORPORATE SOURCE: (1) Lab. of Neuroscience, NIDDK/LN, NIH, Build. 8, Room 111, Bethesda, MD 20892 USA
SOURCE: Journal of Neurochemistry, (1992) Vol. 59, No. 4, pp. 1516-1521.
ISSN: 0022-3042.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Conantokins T and G are polypeptide toxins present in snails of the genus Conus. These substances were recently reported to act as N-methyl-D-aspartate (NMDA) antagonists. In the present study, we examined the possible mechanisms producing this antagonism. Conantokin-G in inhibited spermine- and spermidine-stimulated (3H)MK-801 binding to extensively washed rat forebrain membranes in a noncompetitive manner with IC-50 values of apprx 4507 and apprx 946 nM, respectively. In contrast, **glutamate**-enhanced (3H)MK-801 binding was unaffected by conantokin-G concentrations of ltoreq 20 mu-M. At concentrations gtoreq 5 mu-M, conantokin-G effected a modest, noncompetitive inhibition of glycine-stimulated (3H)MK-801 binding and also produced a small enhancement of basal (3H)MK-801 binding. Conantokin-G reduced (IC-50 apprx 1.08 mu-M) the NMDA-stimulated accumulation of cyclic GMP in cerebellar granule cell cultures to basal values, but did not affect kainate-mediated

increases in cyclic GMP. These findings indicate that conantokin-G acts as a noncompetitive NMDA antagonist through an allosteric inhibition of polyamine responses. The neurochemical profile of this polypeptide is distinct from previously described noncompetitive NMDA antagonists.

L67 ANSWER 11 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:38485 BIOSIS
DOCUMENT NUMBER: PREV200200038485
TITLE: Increased expression of kainate receptors in mouse trisomy 16 cortical neurons: A model of Down syndrome.
AUTHOR(S): KlineBurgess, A. (1); Balbo, A.; **Maccecchini, M. L.** ; Rapoport, S. I.; Galdzicki, Z. (1)
CORPORATE SOURCE: (1) Anatomy, Physiology and Genetic, Medical School, USUHS, Bethesda, MD USA
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 2344. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Ionotropic **glutamate** receptor interactions play a role in neuronal plasticity and neurodevelopment. Trisomy 16 mice (Ts16 and Ts65Dn) are considered models of Down syndrome (human trisomy 21), as the murine chromosome (Chr.) 16 is homologous to the long arm of human Chr. 21. The GluR5 subunit of the kainate (KA) subtype of **glutamate** receptors is coded by a gene localized on human Chr. 21 and mouse Chr. 16. We investigated the expression of the KA receptors using binding and Western blot techniques. Binding of (3H)-(2S,4R)-4-methylglutamate (SYM 2081), a novel KA receptor specific ligand, was quantified in trisomic and diploid mouse fetal cultured cortical neurons and in adult mouse cortical tissue. Fetal Ts16 and diploid neurons were maintained in serum-free Neurobasal/B27 medium for 10-14 days. Binding of (3H)SYM 2081 to the cultured neurons was measured by methods described (Galdzicki et al 1998). Cortical membranes were prepared using Ts65Dn and diploid brains (Toms et al. 1997). Non-specific binding was defined using 1 mM **L-glutamate** . (3H)SYM2081 (1 to 1000 nM) bound in a dose-dependent manner to cortical neurons in cultures and to the cortical membranes preparation. 100 muM KA and 10 muM domoate displaced almost 100% of 5 and 25 nM (3H)SYM2081 binding, 100 muM ATPA (GluR5 specific antagonist) blocked 50% of specific binding. Ts16 cortical neurons and Ts65Dn cortical membranes showed apprx120% and 50% increases in specific binding, respectively. These results indicate an increased expression of KA receptors in trisomy 16 neurons, due to a gene-dosage effect.

L67 ANSWER 12 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:461674 BIOSIS
DOCUMENT NUMBER: PREV200000461674
TITLE: Novel sulfur containing dihydrophthalazine antagonists of AMPA receptors.
AUTHOR(S): Li, Baoqing (1); **Pei, Xue-Feng (1)**; **Maccecchini, Maria (1)**
CORPORATE SOURCE: (1) Department of Medicinal Chemistry, Annovis, Inc, 34 Mt. Pleasant Dr, Aston, PA, 19014 USA
SOURCE: Abstracts of Papers American Chemical Society, (2000) Vol. 220, No. Part 1, pp. MEDI 212. print.
Meeting Info.: 220th National Meeting of the American Chemical Society Washington DC, Washington DC, USA August 20-24, 2000 American Chemical Society
. ISSN: 0065-7727.
DOCUMENT TYPE: Conference
LANGUAGE: English

Searched by Barb O'Bryen, STIC 308-4291

SUMMARY LANGUAGE: English

L67 ANSWER 13 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:80874 BIOSIS
DOCUMENT NUMBER: PREV200100080874
TITLE: Dihydrophthalazines are novel allosteric antagonists of AMPA receptors in hippocampal neurons.
AUTHOR(S): Galdzicki, Z. (1); **Pei, X. F.; Maccecchini, M. L.**; Rapoport, S. I.; Howe, J. R.
CORPORATE SOURCE: (1) USUHS, Bethesda, MD USA
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-339.9. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Excessive activation of AMPA receptors is thought to contribute importantly to excitotoxic injury. To develop new AMPA-receptor antagonists, we have synthesized a novel series of 1,2-dihydrophthalazines. Previous studies have shown that analogs from this series (SYM 2206, SYM 2189, SYM 2229) are effective AMPA receptors antagonists in cerebellar granule cells (Pei et al. 1999) and in spinal cord neurons (Irizarry et al. 1999). Since these compounds may have potential antiepileptic activity, we tested their effectiveness in hippocampal neurons. Whole-cell patch-clamp recordings were made from neurons in primary cultures of mouse embryonic hippocampus. In these neurons, kainate (KA) evoked sustained AMPA-receptor-mediated currents. These KA-evoked currents were blocked by each analog tested. Mean (+- SEM) IC50 values were 3 +- 0.2, 10 +- 2 and 26 +- 7 muM for SYM 2229, SYM 2206 and SYM 2189, respectively (n=5-8 cells). Dihydrophthalazine block of KA-evoked currents was noncompetitive, but was independent of voltage and did not require channel opening. NMDA-evoked responses in the same neurons were unaltered. In contrast to the 2,3-benzodiazepines (e.g. GYKI 53655), AMPA-receptor inhibition by the dihydrothalazines is largely unaffected by cyclothiazide (100 muM). We also found that SYM 2229 (30 muM) blocked spontaneous miniature synaptic currents in a reversible fashion. These results show that the dihydrophthalazines are effective and selective allosteric AMPA receptor antagonists in hippocampal cultured neurons.